Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cidomycin Paediatric 20mg/2ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml vial contains Gentamicin Sulphate equivalent to 20mg Gentamicin base (10mg/ml).

Each 2ml vial also contains less than 1mmol sodium (<23mg).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gentamicin is indicated for the treatment of serious systemic infections including those of the central nervous system due to organisms sensitive to this anti-infective. Such infections include urinary tract infections, chest infections, bacteraemia, septicaemia, severe neonatal infections and other systemic infections due to sensitive organisms.

Gentamicin is usually active against most strains of the following organisms; *Eschericha coli*, *Klebsiella* spp., *Proteus* spp. (indole positive and indole negative) *Pseudomonas aeruginosa*, *Staphylococci*, *Enterobacter* spp., *Citrobacter* spp. and *Providencia* spp.

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

4.2 Posology and method of administration

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.

Renal impairment:
Gentamicin is excreted by simple glomerular filtration and, therefore, reduced dosage is necessary where renal function is impaired. Nomograms are available for the calculation of dose, which depends on the patient's age, weight and renal function. The following table may be useful when treating adults.
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.

Blood urea mg/100ml (mmol/1)	Creatinine clearance (GRF) (ml/min)	Dose and frequency of administration
<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 creatinine (mg%) x 8 or in SI units, as serum creatinine (µmol/1) 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 and intravenous injection. Trough levels give confirmation of adequacy of dosage and also serves to detect levels above 10mg/1, at which the possibility of ototoxicity should be considered. One hour concentrations of gentamicin should not exceed 10mg/1 (but should reach 4mg/1), while the pre-dose trough concentration should be less than 2mg/1.

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.

4.3 Contraindications

Use in patients suffering from Myasthenia Gravis.

Use in patients hypersensitivity to gentamicin or to other aminoglycosides.

Use in early pregnancy unless the physician considers the infection life-threatening.

Use concurrently with other nephrotoxic or ototoxic drug substances.

Gentamicin should not be mixed with any other drug prior to administration.

Intraventricular administration in neonates/infants (aged up to 1 year) is contraindicated (see section 4.4).

4.4 Special warnings and precautions for use

Increased mortality was observed, in neonates/infants (aged up to 1 year) who received gentamicin solution for injection intraventricularly.

Gentamicin should be used with caution in the elderly, those with a history of, or existent ear disease, or those previously on aminoglycosides.

Ototoxicity (including irreversible hearing loss) has been reported following the use of aminoglycosides, including gentamicin. Important risk factors include renal impairment, high doses, prolonged duration of treatment and age (neonate/infant, elderly). Due to the potential for ototoxicity, monitoring of vestibule and cochlea function is recommended before, during and shortly after treatment (see section 4.8).

Gentamicin should only be used during pregnancy if considered essential by the physician.

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.

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).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interactions

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 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.

Aminoglycosides, including gentamicin may induce neuromuscular blockade and respiratory paralysis and should, therefore, only be used with great caution in patients receiving curare muscle relaxants or general anaesthetics.

Indometacin possible increases plasma concentrations of gentamicin in neonates.

Cross-sensitivity with neomycin and kanamycin may occur. Synergistic action has been demonstrated with penicillins.

Concurrent use of the Botulinum Toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.

Concurrent use with oral anticoagulants may increase the hypoprothrombinaemic effect.

Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

4.6 Fertility, pregnancy and lactation

Gentamicin should only be used during pregnancy if considered essential by the physician. 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 risk. In the absence of gastro-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 known

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10%; Common ≥1 and < 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Side-effects include the following:

Ear and labyrinth disorders:
Vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction.

Renal disorders:
Nephrotoxicity (usually reversible) and occasionally acute renal failure

Hepatobiliary disorders:
Effects on liver function occur occasionally.

Immune system disorders:
Not known: anaphylactic reaction (including anaphylactic shock) and hypersensitivity

Blood and lymphatic tissue disorders:
Anaemia, blood dyscrasias, rarely hypomagnesia

Gastrointestinal disorders:
Nausea, vomiting, stomatitis and prolonged therapy and antibiotic-associated colitis have been reported.

Skin and subcutaneous tissue disorders:
Rash, purpura
Not known: Stevens-Johnson syndrome, Toxic epidermal necrosis

Nervous system disorders:
Convulsions occur occasionally. Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression and hallucinations, have been reported in association with gentamicin therapy but this is extremely rare.
Not known Peripheral neuropathy

Vascular disorders
Not known Hypotension

Infections and Infestations
Not known: Superinfection (caused by gentamicin-resistant bacteria),
Pseudomembranous colitis.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Haemodialysis and peritoneal dialysis will aid the removal from the blood, but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockage caused by gentamicin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: S01 AA 11

Gentamicin is a mixture of antibiotic substances produced by the growth of micromonospora purpura. It is bactericidal with greater antibacterial activity than streptomycin, neomycin or kanamycin.

Gentamicin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effect is inhibition of protein synthesis at the level of the 30s ribosomal subunit.

5.2 Pharmacokinetic properties

Gentamicin is not readily absorbed from the gastrointestinal tract. Gentamicin is 70-85% bound to plasma albumin following administration and is excreted 90% unchanged in urine. The half-life for its elimination in normal patients is 2-3 hours.

Effective plasma concentration is 4-8µg/ml.

The volume of distribution (vd) is 0.31/kg.

The elimination rate constant is:

0.02hr $^{-1}$ for anuric patients*
0.30hr $^{-1}$ for normal patients

* Therefore in those with anuria care must be exercised following the usual initial dose, any subsequent administration being reduced in-line with plasma concentrations of gentamicin.

Paediatric Population

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 bodyweightmeans 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

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections
Sodium Chloride
Sodium Hydroxide (for pH adjustment)
Sulphuric Acid (for pH adjustment)

6.2 Incompatibilities

In general, gentamicin injection should not be mixed.

In particular the following are incompatible in mixed solution with gentamicin injection: penicillins, cephalosporins, erythromycin, heparins, and sodium bicarbonate.

* 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.

* Carbon dioxide may be liberated on addition of the two solutions. Normally this will dissolve in the solution, but under some circumstances small bubbles may form.

6.3 Shelf life

Unopened: 2 years.

Opened: Use immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Packs of 5 x 2ml vials.

The vials comprise of Type I Ph Eur clear glass, with a chlorobutyl rubber stopper and aluminium flip-off collar (plus polypropylene disc).

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

For single use only.

Discard any remaining solution after use.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/036/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 31st December 2009

10 DATE OF REVISION OF THE TEXT

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