NOVARTIS

Summary of Product Characteristics

Gentalek Injection 80mg/2ml

v04_04_2018

1. NAME OF THE MEDICINAL PRODUCT

Gentalek Injection 80mg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for injection contains 80 mg gentamicin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of serious infections caused by gentamicin susceptible pathogens.

Fundamental indications for aminoglycosides are infections caused by pathogens resistant to other, less toxic medicinal products as well as serious infections with Gram-negative pathogens, nosocomial infections as well as infections in immunocompromised patients with neutropenia.

Under these circumstances, gentamicin may be used in

- infections of urinary and sexual organs (gonorrhoea and syphilis do not belong to the indications)
- nosocomial pneumonia (since pneumonia in out-patient environment is mainly caused by pneumococci, gentamicin is not the first-line treatment in such cases)
- endocarditis
- intra-abdominal infections
- nosocomial sepsis
- meningitis caused by Gram-negative pathogens osteomyelitis and purulent arthritis
- infections or risk of infection in immunocompromised patients

Note
In the sense of calculated chemotherapy, combination therapy is indicated predominantly with a beta-lactam antibiotic or with an antibiotic effective against anaerobe bacteria in life-threatening infections with unknown pathogen, in mixed anaerobe/aerobe infections, in bacterial endocarditis, in systemic Pseudomonas infections as well as in immunocompromised predominantly neutropenic patients.

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

4.2 Posology and method of administration

Gentamicin may be administered as intramuscular injection and slow intravenous injection or as short-term infusion.

The starting dose is 1.5-2.0 mg gentamicin / kg (body weight: b.w, kg), regardless of kidney function recommended.

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg b.w. 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 b.w. per day as 1 (preferred) up to 2 single doses.

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

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

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

For treatment of neutropenic patients and in endocarditis therapy the total daily dose should be divided into 3 single doses.

In case of combination therapy (e.g. with a beta-lactam antibiotic in the usual dose), administration of the entire daily dose, i.e. once-daily administration, is also possible. Clinical and pharmacological studies in animals have shown that this mode of administration has advantages regarding efficacy and tolerability as compared to administration of several single doses.

Recommendations regarding dose and therapeutic monitoring of gentamicin

Dose (adults)

Initial dose

120 mg gentamicin (1.5-2.0 mg gentamicin/kg b.w.)

Duration of infusion

30-60 minutes

Maintenance dose

3-6 mg gentamicin/kg b.w./day

Dose interval

The dose intervals may be adjusted to the individual half-life. The half-life is calculated according to the concentrations measured (peak and trough levels) either graphically or arithmetically (see example).

Example: half-life

$$t_{1/2} = \frac{\ln 2 \times (t_2 - t_1)}{\ln\left(\frac{C1}{C2}\right)} = \frac{0{,}69 \times 7}{\ln\left(\frac{7}{1}\right)} = \frac{4{,}83}{1{,}95} = 2{,}5 \text{ hours}$$

Withdrawals of blood

It is taken at the end of a dose interval (trough level) and directly after the end of the infusion (peak level). Superelevated trough levels (more than 2 mg gentamicin/l with conventional dosing and more than 1 mg gentamicin/l for a once daily dose) indicate accumulation (nephrotoxicity). Dose interval to be prolonged or dose possibly to be reduced.

Dose in impaired renal function

Gentamicin is excreted mainly via glomerular filtration. The dose must thus be adjusted accordingly in patients with impaired renal function.

There are two possibilities for adjustment of the dose

A: prolonged dose intervals in constant dose (sequential doses identical with initial dose)

B: reduced dose in constant dose intervals (sequential doses <initial dose).

For A: Prolonged dose interval in constant dose

The individual dose intervals (in hours) may be estimated by means of the following equation:

$$T_{ind} = T_N \frac{t_{1/2\,ind}}{t_{1/2\,N}} \quad \text{or} \quad T_{ind} = T_N \frac{Cl_{genta(N)}}{Cl_{genta(ind)}}$$

As the gentamicin clearance is directly proportional to creatinine clearance, the following approximation equation may also be used:

$$T_{ind} = T_N \frac{Cl_{cr(N)}}{Cl_{cr(ind)}}$$

$T_{ind} =$ individual dose interval (hours)

$T_N =$ normal dose interval (mostly 8 hours)

$t_{1/2\ ind} =$ half-life of gentamicin in impaired renal function (determination of half-lives see above)

$t_{1/2\ N} =$ half-life of gentamicin in normal renal function (approx. 2-3 hours)

$Cl_{genta} =$ gentamicin clearance

$Cl_{cr} =$ creatinine clearance

Example
In case of creatinine clearance of 30 ml/min, the dose interval in constant dose would be

$$T_{ind} = 8 \times \frac{100}{30} = 26 \text{ hours}$$

on the basis of $Cl_{cr(N)}$ of 100 ml/min.

For B: Reduced dose in constant dose intervals
As gentamicin is excreted almost exclusively via the kidneys, sequential doses in severely impaired renal function may be estimated according to the following formula:

$$D_{ind} = \frac{Cl_{cr(ind)}}{Cl_{cr(N)}} \times D_N$$

$Cl_{cr(ind)} =$ creatinine clearance in impaired renal function

$D_N =$ normal dose

$D_{ind} =$ sequential dose in impaired renal function

The following table is a guide for reducing the dose in constant dose intervals (8-hour dose interval)

Serum creatinine (mg/100 ml)	Creatinine clearance (ml/min/1.73 m^2)	Sequential doses (percent of initial dose)
<1.0	>100	100
1.1-1.3	71-100	80
1.4-1.6	56-70	65
1.7-1.9	46-55	55
2.0-2.2	41-45	50
2.3-2.5	36-40	40
2.6-3.0	31-35	35
3.1-3.5	26-30	30
3.6-4.0	21-25	25
4.1-5.1	16-20	20
5.2-6.6	11-15	15
6.7-8.0	<10	10

It must be heeded that renal function can alter in the course of treatment.

Creatinine clearance should be preferred as parameter especially in patients with fluctuating plasma creatinine concentrations as observed in severe infections (e.g. sepsis).

If only serum creatinine values are known, creatinine clearance may be estimated according to the following formulas:

Men:

$$Cl_{cr} = \frac{bodyweight\ (kg) \times (140 - years\ of\ life)}{72 \times serum\ creatinine\ (mg/100\,ml)}$$

or

$$Cl_{cr} = \frac{bodyweight\ (kg) \times (140 - years\ of\ life)}{0.814 \times serum\ creatinine\ (\mu mol/l)}$$

For women, the result is multiplied with the factor 0.85.

If serum creatinine values are used to assess renal function, these findings should be made several times, as there is correlation to creatinine clearance values only in constantly impaired renal function.

Dose in haemodialysis patients

Haemodialysis is indicated if creatinine clearance is below 5 ml/min. Gentamicin is dialysable. 50-60% reduced concentration must be expected in 4-5-hour haemodialysis and 70-80% in 8-12- hour haemodialysis. After each dialysis it must be re-dosed on an individual basis, referring to current gentamicin serum concentrations.

The recommended dose after dialysis is usually 1.0-1.7 mg/kg b.w.

As haemodialysis patients generally receive anticoagulants, gentamicin must not be administered by the intramuscular route due to the risk of formation of haematomas.

Method of administration

[Gentamicin – parenteral dosage forms] is suitable for intramuscular, intravenous, subconjunctival injection or intravenous infusion.

The injection/infusion is not to be administered together with other active substances.

In order to avoid high peak concentrations, infusion over a duration of 30-60 minutes is recommended.

Sulphite-free gentamicin solutions, such as *[Gentamicin – parenteral dosage forms]*, may be injected - if medically indicated - undiluted directly into the vein. The injection must be given slowly during 2-3 minutes.

Gentamicin solutions may be diluted for infusion with sodium chloride 9 mg/ml (0.9 %) solution for injection.

In common bacterial infections, the duration of treatment is guided by the course of the disease. A therapeutic duration of 7-14 days is usually sufficient.

The duration of therapy should not exceed 10-14 days if possible.

4.3 Contraindications

Gentamicin must not be used in known hypersensitivity to gentamicin, to other aminoglycosides or any of the excipients.

4.4 Special warnings and precautions for use

Gentamicin should be used in advanced renal insufficiency or preexisting labyrinthine deafness only in vital indication.

As gentamicin has neuromuscularly blocking properties, special attention is required in patients with preexisting neuromuscular diseases (e.g. myasthenia gravis, Parkinson's disease).

The same applies to patients concomitantly receiving muscle relaxants (e.g. in peri-operative administration of gentamicin).

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

- dose strictly according to creatinine clearance. In impaired renal function, the dose must be adjusted to renal performance.
- in impaired renal function, local administration (inhalation, endotracheal instillation) must be considered as well in the total dose in concurrent systemic use.
- therapy-associated monitoring of gentamicin concentrations in serum during therapy in all problematic treatments. Peak concentrations of 10-12 mg/l and trough concentrations of 2 mg/l should not be exceeded for conventional twice daily administration.

Trough concentrations should not exceed 1 mg/ml for a once daily dose.

- therapeutic duration to be limited to 10-14 days if possible
- renewed aminoglycoside therapy to be avoided directly following preceding aminoglycoside treatment, therapy-free interval of 7-14 days if possible
- if possible, no concurrent administration of other potentially ototoxic and nephrotoxic substances; if this cannot be avoided, especially close monitoring of renal function is indicated.
- sufficient hydration and urinary production to be ensured

- 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).

[For injectable products containing FM27 in rubber material, e.g. in removable needle shields or tip caps:]

Latex-sensitive individuals: The [name of the affected part of the product, e.g. removable needle shield] of [product] contains a derivative of natural rubber latex. Although no natural

rubber latex is detected in the [name of the affected part of the product], the safe use of [product] in latex-sensitive individuals has not been studied.

4.5 Interaction with other medicinal products and other forms of interaction

Muscle relaxants and ether

The neuromuscularly blocking properties of aminoglycosides are potentiated by ether and muscle relaxants.

If gentamicin is administered during or directly after surgery, the neuromuscular blockade may be enhanced and prolonged in concurrent use of muscle relaxants of the non-depolarising type. These interactions may be the cause of unexpected incidents. Such patients should especially be monitored due to the aggravated risk.

The neuromuscular blockade induced by aminoglycosides may be reversed by injection of calcium chloride.

Gentamicin/methoxyflurane anaesthesia

Aminoglycosides may enhance the nephrotoxic effect of methoxyflurane. If used concurrently, severest nephropathies are possible.

Potentially ototoxic or nephrotoxic medicinal products

Due to the elevated risk of side effects, patients concurrently or subsequently treated with potentially ototoxic or nephrotoxic medicinal products, such as amphotericin B, colistin, cephalosporins, ciclosporin, cisplatin, vancomycin, loop diuretics such as etacrynic acid and furosemide, should especially be monitored.

It is to be heeded in cisplatin-containing medicinal products that the nephrotoxicity of gentamicin may be potentiated even 3-4 weeks after administration of these substances.

Antibiotics

Combined therapy with suitable antibiotics (e.g. with beta-lactams) may lead to a synergistic effect.

Synergistic effects with acylamino penicillins *on Pseudomonas aeruginosa*, with ampicillin on Enterococci (bacteria) and with cephalosporins on *Klebsiella pneumoniae* have been described.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of gentamicin during pregnancy. Animal studies have shown reproductive toxicity of gentamicin (see section 5.3). Gentamicin crosses the placenta and there is a potential risk of damage of the inner ear and the kidney in the foetus.

Therefore, gentamicin should be used during pregnancy only in vital indications and where safer alternatives are not available.

Breast-feeding

Gentamicin is excreted at low levels in breast milk and low concentrations have been detected in serum of breast-fed infants. If treatment with gentamicin during breast-feeding is inevitable, nursing should be discontinued.

Diarrhoea and fungal infections of mucous membranes may occur in breast-fed infants. The possibility of sensitisation should be borne in mind.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.7 Undesirable effects

The evaluation of undesirable effects is based on the following information on frequency:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Blood and lymphatic system disorder

Altered number of blood platelets (thrombopenia) and of white blood cells (leukopenia, eosinophilia, granulocytopenia) may occur in very rare cases on therapy with gentamicin.

Immune system disorders

Hypersensitivity reactions of different severity may occur, which may range from exanthema and pruritus via drug fever up to severe acute hypersensitivity reactions (anaphylaxis).

Not known: anaphylactic reaction (including anaphylactic shock) and hypersensitivity

Nervous system disorders

Polyneuropathy and peripheral paraesthesia have been described in isolated cases.

Ear and labyrinth disorders

Damage to the auditory nerve (N VIII) is possible, organ of equilibrium as well as of hearing may be affected.

In case of ototoxic reactions, vestibular disorders predominate.

Auditory defects first affect the high frequency range and are mostly irreversible. Most important risk factor is preexisting renal insufficiency. In addition, the risk increases with the level of total and daily dose.
Symptoms of the ototoxic effects are e.g. vertigo, tinnitus, reduced faculty of hearing.

Not known: Irreversible hearing loss, deafness

Renal and urinary disorders

Renal dysfunction is common on gentamicin. Renal dysfunctions such as impaired glomerular filtration rate are observed in approx. 10% of patients and are mostly reversible. The most important risk factors are high total dose, prolonged therapy and elevated serum levels (high trough levels). Furthermore, age, hypovolaemia and shock may be additional risks.

Clinical signs of nephrotoxicity are proteinuria, cylindruria, haematuria, oliguria, elevated creatinine and urea concentrations in serum.

Very rare: Acute renal failure, Fanconi-like syndrome in patients treated with a prolonged course of high-dose

General disorders and administration site conditions

Pain at the site of injection is possible.

Investigations

A syndrome with hypokalaemia, hypocalcaemia and hypomagnesaemia rarely occurs in high-dosed long-term therapy (more than 4 weeks).

A reversible increase in liver enzymes (transaminases, alkaline phosphatase) as well as in bilirubin concentrations in serum has been observed in rare cases.

Infections and infestations

Not known: Superinfection (caused by gentamicin-resistant bacteria), Pseudomembranous colitis

Skin and subcutaneous tissue disorders

Not known: Steven Johnson syndrome, Toxic epidermal necrosis

4.8 Overdose

Gentamicin has a close therapeutic range. In case of cumulation (e.g. due to impaired renal function), nephrotoxicity and damage to the auditory nerve may occur. Nephrotoxicity is correlated with trough levels of more than 4 mg/l.

Therapy in overdose

Discontinuation of the medication. There is no specific antidote. Gentamicin may be removed via haemodialysis.

Therapy in neuromuscular blockade

In case of neuromuscular blockade (mostly caused by interactions, see section 4.5), administration of calcium chloride is advisable, if necessary artificial respiration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, aminoglycoside antibacterials, other aminoglycosides
ATC code: J01GB03

Gentamicin is a parenteral aminoglycoside antibiotic. It represents a mixture of the structurally very similar homologues gentamicin C1, C1a and C2.

Mechanism of action

The mechanism of action of gentamicin is based on the disruption of protein biosynthesis at the bacterial ribosome by interacting with the rRNA and subsequent inhibition of translation. This results in a bactericidal activity.

PK/PD relationship

Efficacy mainly depends on the ratio between the maximum serum concentration (Cmax) and minimum inhibitory concentration (MIC) of the pathogen.

Mechanism of resistance

A resistance to gentamicin may be based on the following mechanisms:

- *Enzymatic inactivation*: the most common mechanism of resistance is the enzymatic modification of the aminoglycoside molecule by acetyltransferases, phosphotransferases, or nucleotidyltranferases usually found on plasmids
- *Reduced penetration and active efflux*: this mechanism of resistance is mainly found in Pseudomonas aeruginosa
- *Change in the target structure*: modification at the ribosomes may be a cause of resistance, resulting from a mutation or synthesis of methyltransferases

There is almost complete cross-resistance of gentamicin with other aminoglycoside antibiotics.

Breakpoints

Gentamicin was tested by using the usual dilution series. The following minimal inhibitory concentrations were determined for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (version 8.0, valid from 2018-01-01)

Pathogen	**Susceptible [mg/l]**	**Resistant [mg/l]**
Enterobacteriaceae[1, 4]	≤2	>4
Pseudomonas spp.[1]	≤4	>4
Acinetobacter spp.[1]	≤4	>4
S. aureus[2], Coagulase-negative staphylococci[2]	≤1	>1
Enterococcus spp.[3] (test for high-level aminoglycoside resistance)	Note	Note
Viridans group streptococci	Note	Note
Corynebacterium spp.	≤1	>1

[1] Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside doses. Most often aminoglycosides are given in combination with beta-lactam agents.

[2] Aminoglycoside breakpoints are based on once-daily administration.

[3] Enterococci are intrinsically resistant to aminoglycosides and aminoglycoside monotherapy is ineffective. There is likely to be synergy between aminoglycosides and penicillins or glycopeptides against enterococci without acquired high-level resistance. All testing is therefore to distinguish between intrinsic and high-level acquired resistance.

[4.] Breakpoints do not apply to *Plesiomonas shigelloides* since aminoglycosides have low intrinsic activity against this species

Note: Gentamicin can be used to screen for high-level aminoglycoside resistance (HLAR).

Negative test

Isolates with gentamicin MIC ≤128 mg/l or a zone diameter ≥8mm. The isolate is wild type for gentamicin and low -level intrinsic resistant. For other aminoglycosides, this may not be the case. Synergy with penicillins or glycopeptides can be expected if the isolate is susceptible to the penicillin or glycopeptide.

Positive test

Isolates with gentamicin MIC >128 mg/l or a zone diameter <8 mm. The isolate is high-level resistant to gentamicin and other aminoglycosides, except streptomycin which must be tested separately if required. There will be no synergy with penicillins or glycopeptides.

Prevalence of acquired resistance in Germany

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary; expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is questionable. Particularly in severe infections or if therapy has failed, microbiological diagnosis is to be attempted with the proof of the pathogen and its sensitivity to gentamicin.

Commonly susceptible species
Gram positive aerobic microorganisms
Staphylococcus aureus
Staphylococcus saprophyticus°
Gram negative aerobic microorganisms
Acinetobacter pittii
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli [#]
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris°
Proteus mirabilis
*Salmonella enterica (*enteritis salmonella*)*
Serratia liquefaciens°
Serratia marcescens
Species for which acquired resistance may be a problem
Gram positive aerobic microorganisms

Staphylococcus epidermidis [+] *Staphylococcus haemolyticus* [+] *Staphylococcus hominis* **Gram negative aerobic microorganisms** *Acinetobacter baumannii* *Morganella morganii* *Pseudomonas aeruginosa*
Inherently resistant
Gram positive aerobic microorganisms *Enterococcus* spp.[§] *Streptococcus* spp.[§] **Gram negative aerobic microorganisms** *Burkholderia cepacia* *Legionella pneumophila* *Stenotrophomonas maltophilia* ***Anaerobic* microorganisms** *Bacteroides* spp. *Clostridium difficile* ***Other microorganisms*** *Chlamydia* spp. *Chlamydophila* spp. *Mycoplasma* spp. *Ureaplasma urealyticum*

° There were no current data available at the time of publishing this table. Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.

[+] Rate of resistance is over 50% in at least one region.

[§] Clinical efficacy for the therapy of Enterococcus and Streptococcus endocarditis in combination with penicillin is documented if no profund resistance (enterococci) present.

[#] In ICUs, the rate of resistance is ≥10%.

5.2 Pharmacokinetic properties

Absorption

Like all aminoglycoside antibiotics, gentamicin is virtually not absorbed from intact intestinal mucosa following oral administration. Its therapeutic use is therefore parenteral, i.e. intravenous or intramuscular.

In intramuscular administration of 1 mg/kg b.w., mean maximum gentamicin concentrations of 3.5-6.4 mg/l are measured after 30-60 minutes. Following intravenous short-term infusion over 15-30 minutes, comparable serum concentrations than after intramuscular administration are measured after one hour.

Therapeutic serum concentrations are generally between 2 and 8 mg/l. Maximum serum concentrations of 10-12 mg/l with conventional multiple daily dosing should not be exceeded. Prior to new administration, the serum concentration after conventional multiple daily dosing should have fallen to below 2 mg/l.

With once daily dosing the trough concentrations should be <1 mg/l.

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular fluid. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults.

The extracellular fluid 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.

The distribution of gentamicin into single organs leads to different tissue concentrations, the highest concentrations are found in renal tissue. Lower concentrations are found in liver and gallbladder, lung and spleen. In cerebral and nervous tissues, no gentamicin can be identified after parenteral administration, and no measurable concentrations are found either in bones in short-term treatment.

Gentamicin has placental patency. Foetal concentrations may be 30% of maternal plasma concentrations. Gentamicin appears in mother's milk in small amounts (with concentrations of 1/3 of that of maternal plasma).

After repeated injection of gentamicin, approx. 50% of achievable plasma concentrations are measured in synovial, pleural, pericardial and peritoneal fluids. Transfer of gentamicin into cerebrospinal fluid is low even in inflamed meninges (up to 20% of the corresponding plasma concentrations).

Plasma protein binding is <10%.

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 halflife 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.

Gentamicin accumulates in the tubular cells of renal cortex. Terminal half-life around 100-150 hours results from release of gentamicin from this deep compartment.

Excretion does not depend on the dose. Far more than 90% of the substance is excreted via the kidneys. In normal renal function, only approx. 2% of the administered dose is eliminated extrarenally. Total clearance is 0.73 ml/min/kg.

In impaired renal function, the elimination half-life is prolonged depending on the degree of renal insufficiency. Maintenance of the usual dose scheme leads to accumulation.

Gentamicin is completely dialysable.

Depending on the duration of dialysis, 50-80% of gentamicin is removed from serum in extracorporeal haemodialysis. Peritoneal dialysis is possible as well with elimination half-lives between 12.5 and 28.5 hours.

5.3 Preclinical safety data

Acute toxicity

Studies of acute toxicity in various animal species did not yield any special sensitivity (see also section 4.9).

Chronic toxicity

In studies of chronic toxicity (i.m. administration) in various animal species, nephrotoxic and ototoxic effects were observed at high doses.

Mutagenic and carcinogenic potential

In mutagenicity studies conducted to date gentamicin did not show any mutagenic effects.

Long-term studies of a carcinogenic potential are not available.

Reproductive toxicity

For the class of aminoglycoside antibiotics there is the potential risk of inner ear lesion and nephropathy of the foetus. There are reports of foetal renal damage in rats and guinea pig following gentamicin treatment of the dams.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylhydroxybenzoate		1.6 mg
Propylhydroxybenzoate		0.2 mg
Sodium metabisufite		1.6 mg
Disodium edetate		0.2 mg
Propylene glycol		16.0 mg
Sulphuric acid for pH adjustment or Sodium hydroxide for pH adjustment		q.s. q.s.

6.2 Incompatibilities

Beta-lactam antibiotics in itro may inactivate gentamicin; therefore they should not be mixed in the same infusion bottle for intravenous administration. Penicillin should not be mixed directly with gentamiicn due to physical and chemical incompatibility. Gentamicin maybe inactivated by beta-lactam antibiotics invitro and less frequently in vivo. This reaction is significant particularly when using carbenicillin and ticarcillin together with gentamicin. The reaction occurs mainly in vitro therefore, gentamicin and beta-lactam antibiotics shoyld not be mixed in the same syringe or infusion bottle

6.3 Shelf-life

5 Years

6.4 Special precautions for storage

Store below 25c

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Gentalek is a solution for injection. The solution is colourless to almost colourless, clear and free of visible particles. The medicine is available in different pack sizes containing 10 ampoules of 80mg/2ml

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

Gentamicin for short term intravenous infusion is to be diluted

- In 100ml of sodium chloride 9mg/ml (0.9%) solution for injection
- Or glucose 50mg/ml (5%)solution for infusion.

The concentration of gentamicin in the solution should not exceed 1mg/ml

7. MARKETING AUTHORISATION NUMBER(S)

NAFDAC REG NO: 04-0220