ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Gentamicin Sopharma 40 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains the active substance gentamicin sulphate, equivalent to 40 mg gentamicin.
Each 2 ml ampoule contains the active substance gentamicin sulphate, equivalent to 80 mg gentamicin.

Excipients with known effect: methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium sulphite, anhydrous.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Colourless to pale yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gentamicin Sopharma solution for injection is indicated in adults, newborns, infants, children and adolescents for short term treatment of serious infections caused by microorganisms susceptible to gentamicin: Gr (-) microorganisms: Escherichia coli, Proteus spp. (indole positive and indole negative), Pseudomonas aeruginosa, Klebsiella-Enterobacter-Serratia spp., Citrobacter spp., Providencia spp., and some Gr (+) microorganisms:
- Severe systemic infections: bacterial septicaemia (including neonatal sepsis and bacterial endocarditis), peritonitis, infections in immunosuppressed patients, patients with tumours, patients with infections after burns;
- Complicated and recidivating infections of the excretory system: urethritis, cystitis, pyelitis, cystopyelitis, pyelonephritis, infections as a result of nephrolithiasis, prostatitis, incl. gonococcal. In initial and non-complicated infections of the urinary system, gentamicin is administered only when the causative agent is not susceptible to antibiotics with lower nephrotoxicity;
- Severe infections of respiratory airways: severe pneumonia or pneumonia with proved causative agent, exacerbation of mucoviscidosis, bronchiectasis and purulent chronic bronchitis, pleural empyema;
- Infections of the central nervous system (including meningitis, meningoencephalitis);
- Ear-nose-and-throat infections: mastoiditis, otitis media and sinusitis, especially those caused by Gram-negative bacteria (incl. Pseudomonas spp.);
- Infections of the genital organs, incl. adnexitis, gonorrhoea, prostatitis, epididymitis;
- Infections of abdominal organs (infections of the biliary duct: cholangitis, cholecystitis, gallbladder empyema, peritonitis; intra-abdominal abscess); complicated abdominal infections, in combination with metronidazole or clindamycine;
- Skin and soft tissue infections: infected wounds, abscesses, cellulitis;
Bone and joint infections – osteomyelitis, septic arthritis;
Brucellosis; felinosis (cat scratch disease); granuloma inguinale; listeriosis; salmonellosis and shigellosis.

For prophylaxis of:
endocarditis caused by streptococci, enterococci, staphylococci;
surgical infections in immunocompromised patients and patients at intensive care departments.

Anaerobes are naturally resistant to aminoglycosides.
Enterococci and streptococci have a low level of natural resistance, which can be overcome by achieving a synergic effect with penicillins.

### 4.2 Posology and method of administration

**Posology**

*Patients with normal renal function*

**Adults**
The recommended daily dose in adults with normal renal function is 3-6 mg/kg body weight daily, administered once (preferred) or divided into 2 doses.

**Paediatric population**
The recommended daily dose in *children and adolescents* with normal renal function is 3-6 mg/kg body weight daily, administered once (preferred) or divided into 2 doses.

The daily dose in *infants* after the first month of life is 4.5-7.5 mg/kg body weight daily, administered once (preferred) or divided into 2 doses.

The daily dose in *newborns* is 4-7 mg/kg body weight daily. Due to the longer elimination half-life in newborns, the required daily dose is given in a single dose.

*Elderly patients*
Initially, the renal function should be assessed. If renal function is impaired, see the dosage in impaired renal function.

*Patients with impaired renal function*
- In patients with impaired renal function, the recommended daily dose has to be decreased and adjusted adequately to the renal function.
- Single administration of the daily dose is not recommended.
- Renal function should be monitored.

The dosage should be determined in accordance with creatinine clearance values and creatinine serum levels.

In cases where determination of gentamicin concentrations in plasma is impossible, the table gives the dosing intervals and daily doses in per cent depending on renal function condition, assessed according to serum creatinine values.

<table>
<thead>
<tr>
<th>Adult patients weight (kg)</th>
<th>Dose (mg)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Serum creatinine (mg %)</th>
<th>Blood urea (mg %)</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 60</td>
<td>80</td>
<td>Over 70</td>
<td>&lt; 1.4</td>
<td>&lt; 38</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>35 - 70</td>
<td></td>
<td>1.4 - 1.9</td>
<td></td>
<td>38 - 63</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>24 - 34</td>
<td></td>
<td>2.0 - 2.8</td>
<td></td>
<td>64 - 84</td>
<td>Every 18 hours</td>
</tr>
<tr>
<td>16 - 23</td>
<td></td>
<td>2.9 - 3.7</td>
<td></td>
<td>85 - 105</td>
<td>Every 24 hours</td>
</tr>
<tr>
<td>10 - 15</td>
<td></td>
<td>3.8 - 5.3</td>
<td></td>
<td>106 - 159</td>
<td>Every 36 hours</td>
</tr>
<tr>
<td>*5 - 9</td>
<td></td>
<td>5.4 - 7.2</td>
<td></td>
<td>160 - 214</td>
<td>Every 48 hours</td>
</tr>
<tr>
<td>60 or &lt;</td>
<td>60</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>
Doses of 1 to 1.7 mg/kg are recommended in adult patients on haemodialysis; the recommended dose in children is 2 mg/kg after each haemodialysis.

**Patients with hepatic insufficiency**
Adjustment of the recommended dose is not required.

**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. The plasma concentration prior to each successive administration should not exceed 2 μg/ml when administering gentamicin twice daily and 1 μg/ml for a daily dose.

**Method of administration: intramuscularly, intravenously.**
Individual daily doses of gentamicin are the same in intramuscular and intravenous administration. The recommended doses refer to *intramuscular* and *intravenous* administration only. It is administered intravenously in case intramuscular administration is impossible. Intravenous administration of gentamicin is recommended in bacterial septicemia or shock, in patients with congestive heart failure, haematological disorders, severe burns, in patients with reduced muscle mass. When administered intravenously, the recommended dose should be administered slowly over 2-3 minutes directly into the vein. Rapid, direct intravenous administration increases initially the risk to reach potentially neurotoxic doses.

**Preparation of solution for infusion**
The solution for infusion is prepared by diluting the single dose with 50 to 200 ml of 0.9% sterile saline solution or another compatible solvent (5% dextrose). In children, the quantity of the solvent should be reduced. The infusion should continue 1.5 to 2 hours.

**Average duration of treatment**: 7-10 days in *intramuscular* administration and 5-7 days in *intravenous* administration.
The therapeutic effect in susceptible microorganisms is manifested 24 to 48 hours after start of administration. In case no therapeutic efficacy is achieved within 3 to 5 days, the treatment should be discontinued. In presence of septic foci requiring surgical drain, or in resistance of microorganisms, it is possible that the infection remains unaffected. In case there is a need for the therapy to continue longer than 10 days (in difficult-to-treat or complicated infections), the benefit/risk ratio should be assessed. Treatment after the 10th day should continue with monitoring of gentamicin serum concentrations, the renal function and the functions of the auditory and vestibular apparatuses.

**4.3 Contraindications**
- Hypersensitivity to the active substance or aminoglycoside antibiotics (a cross sensitivity to antibiotics of this class exists) or to any of the excipients listed in section 6.1;
- Severe renal insufficiency;
- Auditory nerve disorders;
- Botulism;
- Pregnancy.

**4.4 Special warnings and precautions for use**
- Scarification sensitivity test before the treatment is recommended. Gentamicin should not be administered when the antibiogram shows no susceptibility of the causative organisms to it.
- The risk of oto- or nephrotoxicity is related to the administration of higher doses, impaired renal function or prolonged treatment. Advanced age and dehydration are factors that can enhance the risk of a toxic effect. It is recommended that the maximum plasma concentrations of gentamicin do not to exceed 10 μg/ml, because of an increased risk of oto- and nephrotoxicity. When administering
gentamicin twice daily, the plasma concentration should not exceed 2 μg/ml, and in once daily administration - 1 μg/ml, one hour before the next injection. Evidence of dosage toxicity requires dosage adjustment or discontinuation of the treatment with gentamicin. 
- Administration of gentamicin to patients with cochlear and vestibular apparatus disorders is not recommended, or gentamicin should be prescribed with caution.
- For greater safety in elderly patients and in need of gentamicin administration, the renal function should be assessed and creatinine values determined before treatment.
- Monitoring of gentamicin plasma concentrations is also recommended in patients with mucoviscidosis and obesity.
- To avoid occurrence of adverse events, continuous monitoring (before, during and after treatment with gentamicin) of the renal function (creatinine clearance and serum concentration), control of functions of vestibule and cochlea as well as hepatic and laboratory tests are recommended.
- Should cylindrical bodies, erythrocytes, leucocytes, albuminuria, reduced creatinine clearance, increased creatinine values in urine, reduced relative weight, oliguria appear, as well as in progressive azotemia, treatment should be discontinued and the patient immediately hydrated.
- The curare-like effect characteristic of aminoglycosides may lead to myorelaxation, therefore gentamicin should be prescribed with caution in patients suffering from parkinsonism or myasthenia gravis.
- If surgical intervention is required, the anaesthesiologist should be informed that the patient is on gentamicin therapy, because of a risk of neuromuscular block enhancement.
- The elimination half-life of gentamicin in neonates and premature infants is prolonged because of kidney immaturity and underdevelopment, which imposes strict and careful dosing.
- Aminoglycosides are active in alkaline environment.
- Anaerobes are naturally resistant to aminoglycosides.
- Enterococci and streptococci have a low level of natural resistance, which can be overcome by achieving a synergic effect with penicillins.
- Appearance of meningeal irritation, arachnoiditis, polyradiculitis and ventriculitis is possible in isolated cases after intrathecal or intraventricular administration of aminoglycosides.
- Sodium sulphite included as an excipient can in rare cases cause severe hypersensitivity reactions and bronchospasm. Increased sensitivity to sulphites is more frequently observed in asthmatic patients.
- Parahydroxybenzoates included in the product composition can cause allergic reactions (that may be delayed-type reactions) and very rarely bronchospasm.
- This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

- Combining aminoglycoside antibiotics between themselves should be avoided because of enhancement of the oto- and nephrotoxic effects.
- Concomitant administration of gentamicin and other neuro- or nephrotoxic medicinal products: bacitracin, cisplatin, amphotericin B, colistin, vancomycin, indometacin, should be avoided.
- Combination of aminoglycosides with cephalosporins or polymyxins increases the risk of nephrotoxicity.
- Concomitant administration of aminoglycosides and furosemide or etacrylic acid in renal insufficiency increases the otoxic and nephrotoxic risk, especially in its intravenous administration.
- Concomitant administration of gentamicin and peripheral myorelaxants may enhance the neuromuscular block, appearance of apnoea is possible.
- Gentamicin enhances the effect of botuline toxin, therefore its administration in botulism should be avoided.
- It is possible for gentamicin to cause severe respiratory depression in patients receiving anaesthetics or opioids.
- Synergism with regard to chemotherapeutic effect between beta-lactam antibiotics and aminoglycosides has been observed. Antagonism between aminoglycosides and antibiotics with bacteriostatic action (tetracyclines, chloramphenicol, lincosamides) has been established.
- Physicochemical incompatibilities between gentamicin and the following medicinal substances: beta-lactam antibiotics, novobiocin, furosemide, heparin, sodium bicarbonate, are known, therefore gentamicin should not be mixed with them in solutions for injection or infusion.
4.6 Fertility, pregnancy and lactation

Pregnancy
Gentamicin crosses the placental barrier. Product administration during pregnancy is contraindicated because of risk of ototoxicity in the foetus, incl. total irreversible deafness.

Breast-feeding
Small quantities of gentamicin are found in the breast milk, therefore its administration in the period of lactation should be avoided or the medicinal product should be administered only after careful assessment of the benefit/risk ratio. In case any undesirable effects in the breast-fed infant appear, breast-feeding should be discontinued.

4.7 Effects on the ability to drive and use machines

Gentamicin has major influence on the ability to drive and use machines. Driving and use of machines, as well as activities requiring higher attention should be avoided during treatment with gentamicin, because of risk of vertigo, noise in the ears, loss of balance.

4.8 Undesirable effects

Undesirable effects are classified by frequency and organ class system. The frequency according to MedDra corresponds to: 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).

All aminoglycoside antibiotics can cause irreversible hearing disorder with damage to the cochlear and vestibular nerve, they can exert toxic effect on kidneys and can cause neuromuscular block. These undesirable effects are observed more frequently in patients with impaired renal function, in concomitant treatment with other oto- and nephrotoxic medicinal products, in prolonged treatment with gentamicin and/or administration of doses higher than the recommended ones.

Infections and infestations
Development of superinfections caused by gentamicin-resistant microorganisms and fungi is possible.

Blood and lymphatic system disorders
Rare – changes in blood tests: granulocytopenia, thrombocytopenia, leucopenia, anaemia, eosinophilia, hypokalemia, hypocalcemia, hypomagnesaemia.

Immune system disorders
Very rare – hypersensitivity reactions manifested by urticaria, other skin rashes, itching; hypersensitivity reactions in asthmatic patients due to presence of sulphite in the product composition; hypersensitivity reactions due to presence of hydroxybenzoates in the product composition.

Nervous system disorders
Headache and paraesthesia have been observed.
Neurotoxicity: neurotoxicity with manifestations of peripheral neuropathies and of central symptoms, incl. encephalopathy, confusion, lethargy, hallucinations, convulsions and mental depression, is possible to appear after gentamicin administration.
Neurotoxicity: neuromuscular block. More rarely respiratory depression, apnoea and muscle block may be observed due to the neuromuscular blocking effect of aminoglycoside antibiotics.

Ear and labyrinth disorders
Very common - Neuro- and ototoxicity. Toxic effects on the eighth cranial nerve are manifested by reduced hearing, vertigo, tinnitus. Cochlear disorders are initially manifested by loss of hearing to high tones only, and as regards the vestibular system - by vertigo and balance disturbance.
Vascular disorders
Common – oedemas.
Hypotension.

Gastrointestinal disorders
Uncommon - stomatitis, nausea and vomiting, diarrhoea.

Hepatobiliary disorders
Uncommon – Transient increase in the serum bilirubin, transaminases and alkaline phosphatase.

Renal and urinary disorders
Very common – renal function impairment; impaired glomerular filtration, most often reversible 
Nephrotoxicity – initial symptoms of renal disorders are increase in serum creatinine values, 
albumiuria, appearance of erythrocytes, leucocytes and cylinders in the urine, oliguria, azotemia. This 
results in reduced glomerular filtration and electrolyte imbalance followed by acute tubular necrosis. 
Very rare – renal insufficiency.

General disorders and administration site conditions
Atrophy or lipid necrosis at the site of administration.

4.9 Overdose

Symptoms
The overdose symptoms most often are: nausea, vomiting, vertigo, neuromuscular block, apnoea.

Treatment
In overdose with aminoglycoside antibiotics, the patient should be subjected to haemodialysis or 
peritoneal dialysis. In case of a neuromuscular block, intravenous administration of calcium salts or 
neostigmin should be prescribed. Exchange blood transfusion can be performed in neonates.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic administration. Aminoglycosides.
ATC code: J01GB03

Mechanism of action
Gentamicin belongs to the group of aminoglycoside antibiotics. The mechanism of action of 
gentamicin is similar to that of other aminoglycosides: irreversible binding to 30 S ribosome with 
inhibition of protein synthesis and wrong reading of the genetic code; subsequent incorporation of 
wrong proteins in the cytoplasmic membrane, its disorganisation and enhanced permeation of the 
aminoglycoside in the cell.

Pharmacodynamic effects
Aminoglycosides are wide-spectrum antibiotics, especially effective against aerobic and facultatively 
aerobic Gram-negative bacteria such as the Enterobacteriaceae and Pseudomonas aeruginosa. They 
exert a rapid bactericidal effect on susceptible microorganisms. Gentamicin has a bactericidal effect 
on: Pseudomonas aeruginosa, E. coli, Proteus spp. (indole positive and indole negative), Providencia 
spp., Klebsiella-Enterobacter-Serratia spp., Citrobacter freundii and Staphylococcus spp. (incl. 
penicillin- and meticillin-resistant). Gentamicin is also active against the following Gram-negative 
microorganisms: Brucella, Calymmatobacterium, Campylobacter, Francisella, Vibrio and Yersinia, 
Salmonella and Shigella, as well as to some Neisseria isolates.
Of the Gr (+) microorganisms, susceptible also are Listeria monocytogenes and S. epidermidis.
Usually, gentamicin-resistant are Enterococcus spp. and Streptococcus spp.

5.2 Pharmacokinetic properties
Distribution
The volume of distribution (Vd) of gentamicin is almost equivalent to the volume of extracellular body fluid. The body fluid in neonates is 70-75% of the body weight, compared to 50-55% in adults. The extracellular fluid compartment is larger (40% of the body weight compared to 25% of the body weight in adults). Therefore, Vd of gentamicin/kg body weight is affected and decreases with age – from 0.5-0.7 l/kg in premature to 0.25 l/kg in adolescents. The larger Vd/kg body weight means that administration of a higher dose/kg body weight is necessary to achieve adequate peak plasma concentration.

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 half-life is about 2-3 hours. In neonates, elimination rate is reduced due to immature renal function. The elimination half-life is approximately 8 hours in neonates at a gestation age of 26 to 34 weeks compared with about 6,7 hours in neonates at a gestation age of 35 to 37 weeks. Correspondingly, clearance values increase from 0.05 l/h in neonates at a gestation age of 27 weeks to 0.2 l/h in neonates at a gestation age of 40 weeks.

5.3 Preclinical safety data
LD₅₀ in intramuscular administration to rats is 1100 mg/kg, after intraperitoneal administration it is 924 mg/kg, and in mice - 484 mg/kg.
No statistically significant differences in body weight, behaviour and hematological and clinico-chemical tests have been found in subacute and chronic toxicity studies of gentamicin in doses exceeding many times the therapeutic ones. Insignificant transient, predominantly nephrotoxic and hepatotoxic effects, have been established. There are no data of carcinogenicity, mutagenicity and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Disodium edetate
Sodium sulphite, anhydrous (E221)
Sulphuric acid solution (1 mol/l)
Water for injections

6.2 Incompatibilities
In vitro mixing of aminoglycosides with beta-lactam antibiotics and novobiocin should be avoided because of formation of insoluble precipitate and inactivation. Physicochemical incompatibilities between gentamicin and the following medicinal substances: penicillins, cephalosporins, furosemide, heparin, sodium bicarbonate, are known, therefore gentamicin should not be mixed with them in solutions for injection or infusion.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store in the original package to protect it from light.
Store below 25°C. Do not freeze!
6.5 Nature and contents of container

Primary package
Colourless glass ampoules, hydrolytic class 1, with capacity of 1 ml, with a marking for ampoule opening – a colour dot/ring.
Colourless glass ampoules, hydrolytic class 1, with capacity of 2 ml, with a marking for ampoule opening – a colour dot/ring.

Secondary package
10 ampoules in a blister strip of rigid PVC foil, 1 or 10 blister strips in a cardboard box, together with a package leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

SOPHARMA AD
16, Iliensko Shose Str., 1220 Sofia, Bulgaria

8. MARKETING AUTHORISATION NUMBER(S)

20020911

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20.11.2002/18.07.2008

10. DATE OF REVISION OF THE TEXT

March, 2012

The undersigned Svetlozara Stefanova Chilova certify that this is a true translation made by me from Bulgarian into English of the attached Summary of Product Characteristics.
The translation consists of 9 pages.
Translator:
Svetlozara Stefanova Chilova

Round seal of Bulgarian Drug Agency
The Republic of Bulgaria