SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GENTHAVER 80 mg /2 mL IM/IV Solution for Infusion
Sterile

2. KALİTATİF VE KANTİTATİF BİLEŞİM

In each ampoule (2 mL):
Active Substance:
Each 2 mL ampoule contains 135,59 mg gentamicin sulphate equivalent to 80 mg gentamicin.

Excipients:

Methyl paraben (E218)	3,6 mg
Propyl paraben (E216)	0,4 mg
Sodium metabisulfite (E223)	6,4 mg
Disodium EDTA	0,2 mg
Sodium hydroxide	k.m.

Please see section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Solution for Injection
Colorless, clear solution

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Gentamicin exhibits bactericidal activity and is effective against many strains of gram-positive and gram-negative pathogens including Escherichia, Enterobacter, Klebsiella, Salmonella, Serratia, Shigella, Staphylococcus aureus, certain Proteus and Pseudomonas aeruginosa species. Gentamicin is also often effective against antibiotic-resistant strains of these microorganisms such as streptomycin, kanamycin and neomycin. Gentamicin is effective against penicillin-resistant Staphylococci and is rarely effective on Streptococci.

GENTHAVER is indicated for the treatment of the following infections caused by gentamicin-susceptible bacteria:

<u>Severe Gram-Negative Infections</u>
Lower and upper urinary tract infections
Burn and wound infections
Bacteremia, septicemia
Abscesses

Subacute bacterial endocarditis
Respiratory tract infections (Bronchopneumonia)
Neonatal infections
Gynecological infections

Gram-Positive Infections
Bacteraemia
Abscesses
Accident or surgical trauma
Burns and severe skin lesions

4.2. Posology and method of administration

Posology:

The recommended daily dose in adults with normal renal function is 3-6 mg/kg, usually administered in one or two doses per day.

Administration frequency and duration:

Usually, it can be administered with 12-hour intervals. In life-threatening infections, the dosage frequency may be increased to 6 hours or the daily dose may be increased to 5 mg/kg at intervals of 24 hours.

Method of administration:

Gentamicin is usually administered intramuscularly, but may also be administered intravenously if intramuscular administration is not possible (eg in patients with shock or severe burns).

When administered by intravenous route, the recommended dose is administered intravenously or in the rubber tubing of the injection set for at least 2 to 3 minutes. Direct rapid intravenous administration can potentially lead to nephrotoxic concentrations, so it is very important to administer the recommended dose within the recommended time. Alternatively, the recommended dose may be dissolved in 0.9% NaCl or 5% dextrose, but bicarbonate solutions must not be used (see 6.2 Incompatibilities). The solution thus prepared must be administered by infusion for 20 or 30 minutes.

Additional information for special populations:

Renal / Hepatic failure:

In order to reduce the risk of toxicity in renal failure, the recommended daily dose should be reduced and adjusted to renal function. The first dose should be the same as in normal patients, and then the dose range should be adjusted according to the results of renal function tests as follows.

Dose	**Creatinine Clearance (mL / mg)**	**Serum creatinine mmol / L**	**BUN mmol / L**	**Dose Interval**
80 mg	>70	<0,12	<6,5	8 hours
	35-70	0,12-0,17	6,5-10	12 hours
	24-34	0,18-0,25	11-14	18 hours
	16-23	0,26-0,33	15-18	24 hours
	10-15	0,34-0,47	19-26	36 hours
	5-9	0,48-0,64	27-36	48 hours

Pediatric population:
In children (1 year and older) and adolescents, the recommended daily dose is 3-6 mg/kg administered in one or two doses per day.

In infants older than 1 month, the daily dose is 4.5-7.5 mg/kg administered once or twice.

The recommended dose in newborns is 4.5-7.5 mg/kg once a day. Due to the longer elimination half-life in newborns, it is sufficient to administer the required dose once daily.

Geriatric population:
There is evidence that older patients with previous 8th nerve damage or borderline renal function are more susceptible to aminoglycoside toxicity. Therefore, elderly patients should be monitored closely by evaluating gentamicin serum levels, renal function and ototoxicity symptoms during gentamicin treatment.

Gentamicin serum concentration monitoring recommendation
It is recommended to monitor serum concentrations in the elderly, newborns and patients with renal insufficiency. Samples are taken at the end of the dose range (trough level). Gentamicin should not exceed 2 mcg / mL when administered twice a day and 1 mcg / mL when administered once a day. (See 4.4 special warnings and precautions for use).

4.3. Contraindications
GENTHAVER is contraindicated in the following cases:
- People with known hypersensitivity to gentamicin, other aminoglycosides, sodium metabisulfite, methyl paraben and propyl paraben or any of the excipients contained therein,
- In Myastenia Gravis.

4.4. Special warnings and special precautions for use
Patients receiving gentamicin treatment should be kept under close clinical observation due to toxicity potential.

As with other aminoglycosides, gentamicin toxicity is associated with serum concentration. At serum levels above 10 mcg / mL, the vestibular mechanism may be affected.
The risk of toxicity can be minimized by monitoring serum concentrations. Gentamicin serum to ensure that the peak concentration (1 hour) does not exceed 10 µg/mL and the base concentration (1 hour before the next injection) does not exceed 2 µ/mL when administered twice daily and 1 µg / ml when administered once a day. It is recommended to check the levels.

Simultaneous use with other neurotoxic and/or nephrotoxic drugs may increase gentamicin toxicity. Concomitant use with the following drugs should be avoided:
Neuromuscular blocker drugs, succinyl choline and tubocurarin,
Agents with other nephrotoxicity or ototoxicity potential, such as methicillin and cephalosporins,
Potent diuretics, such as etacrynic acid and furosemide,
Other aminoglycosides.

Factors such as diabetes, auditory vestibular dysfunction, otitis media, history of otitis media, previous use of ototoxic drugs and genetically more susceptible to aminoglycoside ototoxicity are factors that increase the risk of toxic effects in patients.

It is recommended that renal function (serum creatinine, creatinine clearance) be monitored continuously (before, during and after treatment), control of vestibule and cochlea functions, hepatic parameters and laboratory parameters to prevent undesirable effects.

GENTHAVER should be used with caution in cases characterized by parkinsonism and other muscle weakness.

Serum concentrations of gentamicin should be closely monitored and dose reduction should be considered in cases of marked obesity.

GENTHAVER should be used with caution in the elderly, in patients with renal insufficiency and in premature infants as renal function is not fully developed.

Sodium metabisulfite in GENTHAVER rarely causes severe hypersensitivity reactions and bronchospasm.

GENTHAVER contains methyl paraben (E218) and propyl paraben (E216). Rarely, it may cause allergic reactions (possibly delayed) and exceptionally narrowing of the bronchi.

This medicinal product contains less than 1 mmol (23 mg) of sodium per 80 mg / 2 mL dose; that is essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction
Antibacterials:
The risk of nephrotoxicity is increased when combined with cephalosporins, especially

cephalotin and cephaloridine, and other aminoglycosides and vancomycin. Monitoring of renal function is recommended when these combinations are used.

Diuretics:
Strong diuretics, such as furosemide and ethacrynic acid, increase the risk of ototoxicity.

Cytotoxics:
Concomitant use with cyclosporine and fludarabine increases the risk of nephrotoxicity.
Concomitant use with cisplatin increases the risk of nephrotoxicity and possible ototoxicity.

Neuromuscular Blockers:
Aminoglycoside antibiotics, including gentamicin, may induce neuromuscular blockade and respiratory paralysis. For this reason, GENTHAVER should be used with caution in patients who are treated with curative muscle relaxants (tubocurarin) and succinylcholine.
Concomitant use with botulinum toxin increases the risk of toxicity due to increased neuromuscular blocking effect.

Concomitant use with botulinum toxin increases the risk of toxicity due to increased neuromuscular blocking effect.

Cholinergic drugs:
Gentamicin antagonizes the effects of neostigmine and pyridostigmine.

Anticoagulants:
Potentiates the action of anticoagulants such as gentamicin, warfarin and phenindione. Concomitant use with oral anticoagulants may increase the hypotrombinemic effect.

Antifungals:
Co-administration with amphotericin increases the risk of nephrotoxicity.

Bisphosphonates:
The use of gentamicin in combination with bisphosphonates may increase the risk of hypocalcemia.

Indomethacin:
Indomethacin may increase plasma concentrations of gentamicin in newborns.

4.6 Pregnancy and lactation
General advice:
Pregnancy category: D

Women with child-bearing potential / Contraception:
There is not enough data.

Pregnancy:
Some studies on animals have been shown to have teratogenic effects. There is not enough data for human use.
Gentamicin passes into the placenta and there is a risk of causing ototoxicity in the fetus. Therefore, the benefit and risk of damage to the fetus should be assessed prior to use during pregnancy.

Lactation:
Gentamicin passes into breast milk in small amounts. It should be decided whether breastfeeding can be stopped because of the risk of serious adverse reactions in the baby, or whether GENTHAVER treatment should be stopped / avoided.

Reproductive ability/Fertility:
No known effect.

4.7 Effects on ability to drive and use machines
The effects of GENTHAVER on drive and machine use are not known.

4.8 Undesirable effects
Adverse reactions are listed in order of frequency as follows: Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000), isolated notices included.

Blood and lymphatic diseases:
Uncommon: Blood dyscrasias, anemia
Rarely: Hypomagnesis (long-term treatment), hypokalemia, hypocalcemia
Unknown: Reversible granulocytopenia

Diseases of the immune system:
Uncommon: Hypersensitivity, urticaria
Very rare: allergic contact sensitization, anaphylactic reactions,

Diseases of the nervous system:
Very rare: Findings of central nervous system toxicity such as encephalopathy, convulsions, confusion, mental depression, lethargy, hallucinations

Ear and inner ear diseases
Unknown: Hearing loss, vestibular damage (especially in patients with previous ototoxic drugs or renal dysfunction)

Gastrointestinal diseases:
Uncommon: Nausea, vomiting, stomatitis
Rare: Diarrhea (in combination antibiotic treatments including gentamicin), antibiotic-induced colitis

Hepato-biliary diseases:
Uncommon: impaired liver function, transient elevations in serum aminotransferase levels, increased serum bilirubin concentration

Skin and subcutaneous tissue diseases:
Uncommon: Skin rashes

Kidney and urinary tract diseases:
Common: Nephrotoxicity (usually reversible)
Uncommon: Acute renal failure
Rarely: Renal tubular dysfunction

Sodium metabisulfite contained in GENTAMICIN may rarely cause severe hypersensitivity reactions and bronchospasm.

Methyl paraben and propyl paraben contained in GENTAMICIN may cause allergic reactions (possibly delayed) and extraordinary bronchospasm.

Reporting of suspected adverse reactions
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose and treatment

Symptoms
As with other aminoglycosides, gentamicin toxicity is associated with gentamicin serum levels above the critical value. In patients with normal renal function, toxic serum levels are not expected to occur (> 10 μg/mL) after administration of the recommended doses. If higher serum levels are achieved due to renal failure, the dose should be reduced.
Symptoms include dizziness, dizziness and hearing loss.

Therapeutic cautions

Hemodialysis or peritoneal dialysis allows gentamicin to be removed from the blood, but hemodialysis is a more effective method. Intravenously administered calcium salts are used to remove neuromuscular blockade caused by gentamicin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials
ATC code: J01GB03

Gentamicin usually shows a bactericidal effect. Although the mechanism of action is not fully elucidated, the most important effect is the binding of ribosomes to 30S subunits in susceptible bacteria and inhibiting protein synthesis.

In general, gentamicin is effective against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria. It is ineffective against fungi, viruses and most anaerobic bacteria.

Gentamycin in vitro, Esherichia coli, Haemophilus influenzae, Moraxella lacunata at a concentration of 1-8 µg/mL. Neisseria, indole positive and indole negative Proteus, Pseudomonas (including many strains of Ps. Aeruginosa), Staphylococcus aureus. S. epidermidis, and Serratia. However, the sensitivity of different species and gentamicin to different strains of the same species shows significant differences in vitro. Furthermore, in vitro sensitivity does not always reflect in vivo activity. Gentamicin has only minimal activity against Streptococci.

Natural or acquired resistance to gentamicin has been demonstrated in both gram-negative and gram-positive bacteria. Gentamicin resistance may be due to reduced permeability of the bacterial cell wall, changes in the ribosomal binding site, or the presence of plasmid-mediated resistance factor acquired by conjugation. Plasmid-mediated resistance allows the resistant bacterium to enzymatically alter the drug by acetylation, phosphorylation and adenylation and can be transferred between the same or different species. Resistance to other aminoglycosides and other antiinfective drugs (chloramphenicol, sulfonamides, tetracycline, etc.) is hardly carried on the same plasmid.

There is cross resistance between gentamicin and other aminoglycosides.

5.2 Pharmacokinetic properties

Absorption:
Gentamicin is absorbed immediately following intramuscular injection. The plasma peak concentration is reached after 30 minutes to 1 hour. The effective plasma concentration is 4-8 µg/mL and remains within the effective concentration range for 4 hours. A plasma peak concentration of 4 µg/mL is obtained after administration at a dose of 1 mg/kg.

Distribution:
The binding rate to plasma proteins is low (<10%). The dispersion volume is 0.3 L/ kg. The volume of dispersion is approximately equal to the volume of extracellular fluid.

Biotransformation:
No more than 90% of the given dose is biotransformed.

Eliimination:
More than 90% of the administered dose is excreted in the urine by glomerular filtration unchanged. Elimination half-life is 2-3 hours in patients with normal renal function.

Linearity / non-linearity:
Not available.

Characteristics of patients
Renal failure:
Elimination half-life is prolonged in renal failure

Pediatric population:
Premature babies and newborns:

Distribution: The extracellular compartment volume in newborns is 40% of body weight and is higher than in adults. Therefore, the distribution volume in premature newborns is 0.5-0.7 L/kg and it is higher than in adults. Higher doses of gentamicin (mg/kg) are required in premature newborns due to the higher distribution volume.

Elimination: Elimination rate is decreased in newborns due to underdeveloped renal functions.
The mean elimination half-life of newborns at gestational age of 26-34 weeks is 8 hours, whereas it is 6.7 hours for 35-37 weeks gestation age.
Consistent with these values, the clearance value (0.2 L/h) was higher in newborns at the age of 40 weeks gestation than newborns at the age of 27 weeks (0.05 L/h).

5.3 Preclinical safety data
No preclinical safety data is available, other than those explained in other parts of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl paraben (E218)
Propyl paraben (E216)
Sodium metabisulfite (E223)
Disodium EDTA
Sodium Hydroxide
Water for Injection

6.2 Incompatibilities

GENTHAVER must not be mixed with other drugs before injection.

It is incompatible with penicillins, cephalosporins, erythromycin, sulfadiazine, furosemide, heparins and sodium bicarbonate in the same solution. If it is necessary to use with them, it is administered to the IV set tubing in the form of bolus injection, making sure that adequate washing is provided or applied to different areas.

Carbenicillin and gentamicin can only be used together if administered from different sites. The addition of GENTHAVER to solutions containing sodium bicarbonate causes carbon dioxide to be released

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 30°C.

6.5 Nature and contents of container

Each box contains 1, 5, 50 or 100 ampoules of 2 mL made of Type I glass (hospital packaging).

6.6 Instructions for use and handling and disposal

Unused products or waste materials must be disposed of in accordance with the “Medical Waste Control Regulation” and the “Packaging and Packaging Waste Control Regulation”.
Each ampoule is for single use only.
The solution should be used immediately after first opening.
Unused solutions should be discarded.

7 MARKETING AUTHORISATION HOLDER

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191/99

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