1.3.1	Gentamicin sulphate
SPC, Labeling and Package Leaflet	AM

1. NAME OF THE MEDICINAL PRODUCT

Gentamicin-K 40 mg/1 ml solution for injection
Gentamicin-K 80 mg/2 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

40 mg/1 ml solution for injection
1 ml of solution for injection contains 40 mg gentamicin as 66.65 mg gentamicin sulphate. One ampoule (1 ml of solution for injection) contains 40 mg gentamicin as 66.65 mg gentamicin sulphate.

80 mg/2 ml solution for injection
1 ml of solution for injection contains 40 mg gentamicin as 66.65 mg gentamicin sulphate. One ampoule (2 ml of solution for injection) contains 80 mg gentamicin as 133.33 mg gentamicin sulphate.

Excipients:

	1 ml of solution	2 ml of solution
methyl parahydroxybenzoate (E218)	1.8 mg	3.6 mg
propyl parahydroxybenzoate (E216)	0.2 mg	0.4 mg
sodium metabisulphite (E223)	3.2 mg	6.4 mg

For a full list of excipients, see section 6.1.

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3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to slightly yellow solution, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gentamicin-K is indicated in adults and children of all age groups (preterm infants, newborn infants, infants, children, adolescents).

Gentamicin-K (gentamicin) is used for the treatment of severe systemic infections caused by aerobic Gram-negative bacteria susceptible to gentamicin. These infections include:
- sepsis and other severe systemic infections – meningitis, peritonitis (usually in combination with beta-lactam antibiotics),
- intra-abdominal infections: abscesses, cholangitis (usually in combination with metronidazole or clindamycin),
- infections of the urinary tract and respiratory tract,
- secondary infections of burns, traumatic and surgical wounds,
- tularaemia,
- respiratory infections (pneumonia, lung abscess),

- endocarditis (usually in combination with a beta-lactam antibiotic).

Gentamicin-K is also used for the prophylaxis of postoperative infections in intra-abdominal surgery, especially urinary tract and intestinal surgery. In intestinal surgery, a single dose of gentamicin is administered in combination with metronidazole or clindamycin.

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

4.2 Posology and method of administration

Posology

Because of the long post-antibiotic effect of gentamicin, the efficacy of each subsequent dose administered during the period of the post-antibiotic effect is weaker because the bacteria are less susceptible to the effect of gentamicin in this period. Therefore, a single daily dose has a double advantage regarding the antibacterial efficacy of gentamicin:

- a more potent bactericidal effect due to the high initial serum concentrations of gentamicin,
- a better antibacterial effect of the subsequent dose because of a longer dosing interval.

Single daily dosing of gentamicin is not recommended for patients with a weakened immune system (neutropenia), severe renal impairment, cystic fibrosis, ascites, infectious endocarditis, patients with extensive burns (involving more than 20% of the skin surface) and pregnant women.

Adults

The recommended daily dose in adults with normal renal function is 3 mg to 6 mg per kg body weight intramuscularly or intravenously as 1 (preferred) to 2 doses.

When gentamicin is administered in several daily doses, the initial adult dose, regardless of the renal function, is 1.5 mg to 2 mg/kg body weight, which ensures the maximum appropriate serum levels.

Elderly

In elderly patients (65), the dose has to be adjusted to the renal function (see *Patients with renal insufficiency*).

There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity whether secondary to previous eighth nerve impairment or borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function and signs of ototoxicity.

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Paediatric population

Children and adolescents

The recommended daily dose in children and adolescents with normal renal function is 3 mg to 6 mg per kg body weight intramuscularly or intravenously as 1 (preferred) to 2 doses.

Infants (over 1 month of age)

The daily dose in infants after the first month of life is 4.5 mg to 7.5 mg per kg body weight intramuscularly or intravenously as 1 (preferred) to 2 doses.

Newborn infants

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

In newborn infants, infants and children, the same doses determined according to body weight result in lower serum concentrations of gentamicin than in adults. Hence, somewhat higher therapeutic doses are required in these patient groups. For safety reasons, it is recommended that serum gentamicin levels be determined on a daily basis in children. One hour after the administration of gentamicin, its serum levels should be at least 4 µg/ml.

If the daily dose of gentamicin is administered in several doses, the level of gentamicin in the serum should not be more than 2 µg/ml before the administration of the next dose. If the daily dose is administered as a single dose, serum gentamicin levels should not be more than 1 µg/ml.

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

Gentamicin dosage in patients with impaired renal function:

Urea		Creatinine clearance		Serum creatinine		Doses and dosing intervals
mg/100 ml	mmol/l	ml/min	ml/s	mg/100 ml	µmol/l	
<40	<6.8	>70	>1.16	<1.4	<124	80 mg* every 8 hours
40–100	6.8–17	30–70	0.5–1.16	1.4–1.9	124–168	80 mg* every 12 hours
				1.9–2.8	168–248	80 mg* every 18 hours
100–200	17–34	10–30	0.16–0.5	2.8–3.7	248–327	80 mg* every 24 hours
				3.7–5.3	327–469	80 mg* every 36 hours
>200	>34	5–10	0.08–0.16	5.3–7.2	469–636	80 mg* every 48 hours

*60 mg, if body weight <60 kg.

A reduction in dosage and extension of the dosing interval are equally suitable; however, it should be borne in mind that doses determined in such a way are approximate and that the same doses may result in different concentrations in various patients. Therefore, in patients with a complex clinical picture, serum gentamicin concentrations should be measured and the dosage adjusted accordingly. Serum gentamicin concentrations measured 30 to 60 minutes after intravenous or intramuscular administration should be at least 5 µg/ml.
After haemodialysis is completed, 1 mg to 1.5 mg gentamicin per kg body weight should be administered.
In peritoneal dialysis, 1 mg gentamicin per kg body weight should be added to 2 litres of the dialysing fluid.

Duration of treatment: 7 to 10 days or longer in very severe and complicated infections.

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.

Method of administration
Gentamicin is administered intramuscularly or intravenously. In both cases, the same dose should be used. Gentamicin is administered over 2 to 3 minutes either directly intravenously or through a catheter inserted into a vein. When the total daily dose of gentamicin is administered in a single dose, it is injected over 30 to 60 minutes.
For a short intravenous infusion, gentamicin should be dissolved in 100 ml to 200 ml of sterile physiological salt solution, or sterile 5% glucose. The concentrations of gentamicin in the solution should not exceed 1 mg/ml.

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4.3 Contraindications

Hypersensitivity to the active substance, any of the excipients or other aminoglycosides, and

myasthenia gravis.
- neuritis of the auditory nerve;
- myasthenia gravis;
- severe renal insufficiency with uremia and azotemia;
- period of newborn and premature babies (due to the high risk of ototoxicity and nephrotoxicity);
- pregnancy and lactation.

4.4 Special warnings and precautions for use

Patients treated with gentamicin should be under close clinical observation because gentamicin, like other aminoglycosides, exerts nephrotoxic effects, damages the auditory and vestibular systems, and inhibits the neuromuscular transmission. Attention should be paid to hearing impairment, vertigo and tinnitus.

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinine, creatinine clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

Caution should also be used in patients with hypocalcaemia.

In patients with severe renal impairment and in elderly patients (over 65 years of age), dosage should be adjusted according to renal function. Good hydration should be provided.

Special caution should be exercised in patients with myasthenic syndrome or Parkinson's disease because blockade of neuromuscular transmission may occur. This blockade may be prevented by slower intravenous administration.

In overweight patients, gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

After long-term therapy with gentamicin the resistance of microorganisms may develop, in that case the treatment should be discontinued.

The use of a single daily dose is not recommended for patients with: neutropenia, severe renal impairment, cystic fibrosis, abscesses, infective endocarditis, massive burns (more than 20% of the surface of the skin).
Gentamicin-K contains propyl parahydroxybenzoate (E216) and methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
Sodium metabisulphite (E223) may rarely cause severe hypersensitivity reactions and bronchospasm.
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 interaction

Certain potent diuretics (ethacrynic acid and furosemide) enhance the deleterious undesirable effects of gentamicin because the concurrent administration increases the serum and tissue concentrations of the antibiotic. Intravenous administration of diuretics increases the risk of renal damage and auditory and vestibular damage.

If gentamicin is administered concurrently with neuromuscular blocking agents (succinylcholine or tubocurarine), the blockade of neuromuscular transmission is enhanced and respiratory paralysis may occur. The antidotes are calcium and neostigmine.

Gentamicin should not be administered together with other neurotoxic and nephrotoxic drugs, especially amikacin, tobramycin, vancomycin, cephaloridine, viomycin, polymyxin B, netromycin, neomycin and streptomycin.

Concurrent administration of gentamicin and amphotericin B, cyclosporine, cisplatin, clindamycin, piperacillin, methoxyflurane, foscarnet or intravenous radiocontrast agents increases the risk of renal damage and auditory and vestibular damage.

4.6 Fertility, pregnancy and lactation

Pregnancy
Gentamicin crosses the placenta and can cause damage to the auditory and vestibular systems of the foetus. Gentamicin-K should not be used in pregnant women unless it is clearly needed. i.e. in life-threatening situations when there is no other suitable antibiotic available.

Breast-feeding
Gentamicin is excreted in breast milk. Breast-feeding mothers are therefore advised not to breast-feed.

Fertility
Animal studies showed that gentamicin does not affect fertility and reproductive functions (see section5.3).
There are no clinical data on the effect of Gentamicin-K on fertility.

4.7 Effects on ability to drive and use machines

Gentamicin has no influence on psychophysical performance. In individual cases, it can cause transient balance disorders. The condition may worsen even after discontinuation of treatment; therefore, the patient should be warned about this.

4.8 Undesirable effects

Gentamicin is toxic to the auditory and vestibular systems, kidneys and it inhibits neuromuscular transmission. Other possible undesirable effects include: hypersensitivity reactions, elevated body temperature, proteinuria, headache, fatigue, paraestehsias, visual disturbances, palpitations, increased urea, creatinine and bilirubin levels, and increased transaminase activity. The possibility of persistent diarrhoeas due to superinfection with resistant bacteria (pseudomembranous colitis) has also been reported.

Undesirable effects that may occur during treatment with gentamicin are classified into the following groups in order of 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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	Uncommon	Rare	Very rare
Blood and lymphatic system disorders			eosinophilia, neutropenia, thrombocytopenia, anaemia, reduced haemoglobin levels

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Immune system disorders		hypersensitivity reactions (rash)	anaphylactic reaction
Metabolism and nutrition disorders		hypocalcaemia, hypokalaemia, hypomagnesaemia	
Nervous system disorders		neuromuscular transmission blockade**	headache, fatigue, paraesthesia
Eye disorders			visual disturbances
Ear and labyrinth disorders	hearing and balance impairment*, feeling of pressure in the ears, nystagmus, vertigo		
Gastrointestinal disorders	nausea, vomiting, diarrhoea		persistent diarrhoea (pseudomembranous colitis)
Hepatobiliary disorders			increased bilirubin levels and elevated transaminases; these two undesirable effects are indicative of hepatic impairment
Renal and urinary disorders	increased urea and creatinine levels***, proteinuria		
General disorders and administration site conditions			elevated body temperature, palpitations

*The risk of hearing impairment is greater if serum gentamicin concentrations constantly exceed 2 µg/ml. Occasionally higher concentrations are irrelevant to the occurrence of impairment unless they are greater than 10 µg/ml. Vestibular and auditory dysfunction is infrequent but it is important because it is usually irreversible. It may exacerbate even after gentamicin is discontinued. First the high frequency hearing is affected. Impairment is detected by audiometry before clinical signs appear. The first signs are tinnitus and a feeling of pressure in the ears. Vestibular dysfunction is clinically manifest as nausea, vomiting, vertigo or nystagmus. Hearing impairment has been established by audiometry in 22% of patients. Patients at greater risk of auditory and vestibular dysfunction are those who have already had such a dysfunction, patients with renal function impairment, patients who have been treated with other ototoxic drugs, patients who are not adequately hydrated or those who have been treated with higher doses of gentamicin for a long time.
**It mainly occurs with rapid intravenous administration or when large doses of gentamicin are administered into the pleural or peritoneal cavity.
***Gentamicin nephrotoxicity is more common if serum gentamicin concentrations constantly exceed 2 µg/ml, in elderly patients, women, patients with renal impairment, poorly hydrated patients, patients with nephrotic syndrome, patients with diabetic nephropathy, and in those treated with other nephrotoxic agents. The impairment is reversible. It is characterised by increased serum creatinine levels. It can be avoided by providing adequate hydration.

If severe undesirable effects occur, treatment should be discontinued.

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4.9 Overdose

Overdose may result in irreversible impairment of the auditory-vestibular system, transient aggravation of renal function and neuromuscular blockade. Close monitoring of mainly respiration, audiogram and vestibulogram, diuresis and serum concentrations of gentamicin, urea, creatinine,

calcium, magnesium and potassium is required. The patient should be well hydrated. Neuromuscular blockade may be reduced by injecting calcium and neostigmine. The elimination of gentamicin from the body may be precipitated by haemodialysis, especially when renal insufficiency is present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other aminoglycosides; ATC code: J01GB03.

Mechanism of action

Gentamicin inhibits protein synthesis in the bacterial cell by binding to the larger and smaller ribosome subunits. It probably also actively penetrates through the cell wall into the bacterium. Thus the concentrations of gentamicin in the bacterial cell are very high, significantly higher than the concentrations in its surroundings, which enables bactericidal action. Under anaerobic conditions, increased osmolarity and a low pH, the gradient is lower, the passage is hindered and a relative resistance of the bacterium to gentamicin develops. High calcium and magnesium concentrations also inhibit the passage of gentamicin into the bacterium.
Gentamicin can, at concentrations achieved in the renal cortex and perilymph fluid of the inner ear, reduce the synthesis of microsomal proteins. This is how the toxicity in humans is explained.

Pharmacodynamic effects

Gentamicin exerts bactericidal action.

Clinical efficacy

Gentamicin is active against aerobic Gram-negative bacteria, staphylococci and *Listeria monocytogenes*.

Gentamicin-susceptible Gram-negative bacteria are:

- almost all enterobacteria: *E. coli, Enterobacter* spp., *Klebsiella, Proteus* (indole-positive, indole-negative), *Salmonella, Shigella, Providencia, Serratia, Citrobacter, Hafnia, Edwardsiella and Arizona* spp.,
- *Pseudomonas aeruginosa*,
- *Brucella, Moraxella, Pasteurella multocida, Francisella tularensis, Acinetobacter calcoaceticus, Aeromonas* spp.,
- *Campylobacter pylori, C. jejuni*.

Gentamicin is also active against some Gram-positive bacteria:

- *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus* spp. (including penicillin- and methicillin-resistant strains),
- *Listeria monocytogenes*.

The table below shows MICs for some bacteria:

Bacterium	MIC µg/ml
E. coli	1.0–4.0
Klebsiella aerogenes	1.0–2.0
Klebsiella (other spp.'s)	0.06–1.0
Proteus mirabilis	2.0–8.0
Proteus vulgaris	1.0–4.0
Morganella morganii	1.0–4.0
Providencia rettgeri	0.5–4.0
Salmonella spp.	0.25–1.0
Pseudomonas aeruginosa	1.0–8.0
Staphylococcus aureus	0.12–1.0
Listeria monocytogenes	1.0–8.0

Resistance

Bacterial resistance to gentamicin is based on at least three mechanisms: ribosomal mutation, inefficient penetration of gentamicin into the cell and breakdown of gentamicin with various enzymes.
When gentamicin was introduced into treatment, only a small number of enterobacteria were resistant to the drug. As a result of frequent use, especially in intensive care units and burns wards, the number of resistant enterobacteria increased. It is typical that the resistance rapidly decreases if a certain hospital unit or hospital restricts the use of gentamicin.
Resistance to gentamicin very rarely develops during treatment.

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5.2 Pharmacokinetic properties

Absorption

Intramuscularly administered gentamicin is rapidly and completely absorbed and reaches peak serum levels in 30 to 90 minutes. Poor muscle perfusion reduces the absorption.
After an infusion over 20 to 30 minutes, serum concentrations are the same as those obtained by intramuscular administration of an equal dose.
Gentamicin is rapidly absorbed after intraperitoneal or intrapleural administration. After intrathecal or intraventricular administration, it is almost not absorbed.
The average maximum serum concentration following intramuscular administration of 80 mg gentamicin is 7 µg/ml in 0.5 to 2 hours. If the dose is doubled, the maximum concentration doubles, too. The optimal maximum concentration is 7 to 10 µg/ml.
In a newborn infant under 7 days of age, the maximum serum concentration of 4 µg/ml is achieved after a dose of 2.5 mg/kg body weight in 30 to 60 minutes.
With once-daily dosing, the maximum concentrations are higher than those obtained with three-times-daily dosing. According to reports, the toxicity is lowest at concentrations between 10 and 15 µg/ml. Before administering the next dose, the concentration should never be more than 2 µg/ml.

Distribution

Gentamicin is poorly protein-bound (25%); only if calcium and magnesium serum concentrations are low, up to 70% gentamicin may be bound to proteins.

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of body weight, 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 body weight 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 body weight means that for adequate peak blood concentration a higher dose per kg body weight needs to be administered.

Gentamicin passes into the interstitium of nearly all organs. It penetrates well into erythrocytes, neutrophils and especially into the cells of proximal renal tubuli, where its concentrations exceed the serum concentrations.
The half-life of gentamicin is 1.5 to 5.5 hours in healthy young subjects, 1 hour in older children, and 2.3 to 3.3 hours in newborn infants.
In bronchial secretion, gentamicin reaches only 25% of its serum concentrations.
The concentrations of gentamicin reached in liquor are very low in adults. They are somewhat higher in the presence of meningeal inflammation and in newborn infants.
Gentamicin penetrates well into the cornea and aqueous humour, but poorly into the vitreous humour. It reaches 25 to 50% of the serum concentrations in synovial fluid.
Only minute concentrations are found in the prostate and saliva. In the bile, it reaches 25 to 88% of the serum concentrations.

Extremely high concentrations of gentamicin are found in the urine (25 to 100 times the serum concentrations). Gentamicin has been shown to penetrate the heart muscle, liver, muscles and kidneys, where 40% of the total quantity of the antibiotic in the body is accumulated.
Foetal serum gentamicin concentrations reach up to 40% of the maternal serum concentrations. Minute quantities of gentamicin are excreted in human milk.

Metabolism and 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.
Gentamicin persists in tissues long after discontinuation of therapy.
Renal impairment inhibits elimination. Haemodialysis reduces serum gentamicin concentration by about half. Gentamicin can also be removed from the body by peritoneal dialysis.

5.3 Preclinical safety data

Acute toxicity studies demonstrated low toxicity of gentamicin in mice, rats, rabbits, guinea pigs and monkeys: the LD_{50} values were between 20 mg/kg and 180 mg/kg after intravenous administration, and between 430 mg/kg and 780 mg/kg after intramuscular administration. After repeated administration (up to 50 days) of gentamicin at doses up to 200 mg/kg/day to rats, rabbits, dogs, guinea pigs and monkeys, it was found that toxic effects occur mainly in the kidneys and ears. It is assumed that toxic effects occur due to the accumulation of gentamicin. After repeated parenteral administration of injections, local toxic effects occur at the site of administration.
Gentamicin does not affect fertility and reproductive functions; it was found to be embryotoxic in laboratory animals.
Gentamicin has no mutagenic and carcinogenic potential.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

methyl parahydroxybenzoate (E218)
propyl parahydroxybenzoate (E216)
disodium edetate
sodium metabisulphite (E223)
water for injections

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6.2 Incompatibilities

Beta-lactam antibiotics can inactivate gentamicin *in vitro*; therefore, they should not be mixed together in the bottle for intravenous administration. Gentamicin should also not be mixed with erythromycin, heparin and sodium hydrogen carbonate.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

40 mg/1 ml: 10 ampoules of 1 ml of solution for injection, in a box.
80 mg/2 ml: 10 ampoules of 2 ml of solution for injection, in a box.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

Dissolve gentamicin for short-term intravenous infusion in 100 to 200 ml of sterile physiological solution or sterile 5% glucose. The concentration of gentamicin in the solution should not be more than 1 mg/ml.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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