SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANTOKSİ-C 500 mg/5 ml Solution for I.V. Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each ampoule(5 ml) contains 500 mg vitamin C (ascorbic acid). There is 100 mg active substance in unit dosage (1 ml).

Excipients:
In eqach ampoule:

Metyl paraben (E218)	4 mg
Propyl paraben (E216)	0,5 mg
Sodium hydroxide	q.s.

See: section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Solution for injection.
Sterile and clear solution in transparent glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutical indications

It is used in vitamin C deficiency where parenteral treatment is required.

4.2 Posology and method of administration

Posology/Frequency and Duration of administration:
In adults and children over 12 years old: 500 mg - 1000 mg per day. It should not be used more than 2 ampoules (1000 mg vitamin C/day) per day. Preferably, oral use should be given priority. Otherwise, the injection should be applied by healthcare professionals.

Method of administration:
Administered as intravenously.

Additional information on special populations:
Renal / Liver failure:
It is contraindicated in patients with severe renal impairment or impaired renal function (see section 4.3). No specific dose recommendations have been made for patients with liver failure.

Pediatric population:
It is not recommended for use in infants and children.

Geriatric population:
No specific dose recommendations have been made.

4.3. Contraindications

- In patients with known hypersensitivity to the active substance or any of the excipients listed in section 6.1,
- Patients with severe renal impairment (creatinine clearance <30 ml/min) or renal dysfunction, including those undergoing dialysis.
- People who have nephrolithiasis or a history of nephrolithiasis,
- Hyperoxaluria,
- In hemochromatosis: Chronic use of high doses of vitamin C (>500 mg/day in adults) may aggravate iron overload and cause organ damage in patients with hemochromatosis.

4.4 Special warnings and precautions for use

- Acute and chronic vitamin C intake from all sources increases the risk of adverse reactions in children 9-13 years old >1200 mg/day, young adults 14-18 years old >1800 mg/day and adults >2000 mg.
- Acute and chronic vitamin C overdose (>2 g/day) can significantly increase the levels of oxalate in serum and urine. In some cases, this can lead to hyperoxaluria, calcium oxalate crystalluria, calcium oxalate accumulation, kidney stone formation, tubulointerstitial nephropathy and acute renal failure.
- Those with mild or moderate renal impairment may be sensitive to the toxic effects of vitamin C at low doses and the product should be used with caution.
- Vitamin C overdose (>3 g/day in children and >15 g/day in adults) can lead to oxidative hemolysis or diffuse intravascular coagulation in patients with glucose-6-phosphate dehydrogenase deficiency.
- Patients who are prone to calcium-oxalic kidney stone disease or have recurrent kidney stone disease should reduce their vitamin C consumption to 100-200 mg/day.
- Because vitamin C increases iron absorption, high doses can be dangerous in patients with thalassemia, polycythemia, leukemia or sideroblastic anemia.
- It has been demonstrated that high doses of vitamin C are associated with sickle cell crises in sickle cell anemia patients.
- Vitamin C is thought to be able to exacerbate rapidly multiplying and widely spread tumors. Therefore, caution should be exercised when prescribing ascorbic acid in advanced cancers.
- Theoretically, high doses of vitamin C can cause gouty arthritis in susceptible patients due to its effect on uric acid excretion.
- Patients taking other single vitamins or multivitamin preparations, other medications, or under medical care should consult a healthcare professional before taking this product (see sections 4.5 and 4.9).
- Vitamin C may interact with the test kits and measuring device used to measure glucose levels, leading to false readings. Consult the instructions for use of the test kit or meter for guidance (see section 4.5).
- Vitamin C can interact with laboratory tests, leading to false readings. Inform your doctor or healthcare professional when purchasing this product and planning laboratory tests. (see section 4.5).

This medicinal product contains less than 1 mmol (23 mg) sodium per "dose"; in other words, it does not “contain sodium”.

Since ANTOKSİ-C contains methyl paraben (E218) and propyl paraben (E216), it may cause allergic responses (possibly delayed) and unexpected narrowing of the bronchi.

4.5 Interactions with other medical products and other forms of interaction

Various potential interactions have been reported in the literature for individual components. Therefore, patients who use any other medication, take nutritional supplements, or undergo medical treatment should consult a physician or healthcare professional before taking this product.

Drug interactions

Warfarin: High doses of vitamin C may interfere with the effectiveness of warfarin.

Dicumarol: There is an exceptional case in which prothrombin time is shortened after intake of vitamin C.

Disulfiram: Chronic or high doses of vitamin C may interfere the effectiveness of disulfiram.

Desferroxyamine: Vitamin C can increase tissue iron toxicity, especially in the heart, causing cardiac insufficiency.

Cyclosporine: An antioxidant supplement, including vitamin C, can reduce cyclosporine levels in the blood.

Indinavir (protease inhibitors): Since high dose of vitamin C significantly reduces the concentration of indinavir serum, it may prevent the effectiveness of indinavir.

Ethinylestradiol: Vitamin C at a daily dosage of 1 gram may increase the bioavailability of ethinylestradiol from oral contraceptive preparations, which may increase adverse effects from ethinylestradiol. If ethinylestradiol is used simultaneously in the treatment with ascorbic acid, the patient should be monitored for the adverse effects of ethinylestradiol.

Acetylsalicylic acid: In concurrent use, an increase in urinary excretion of vitamin C and a decrease in excretion of acetylsalicylic acid occur. It has been found that acetylsalicylic acid reduces vitamin C absorption by approximately 1/3.
These effects are dose-dependent and vitamin C supplements may be necessary in people who chronically use high doses of acetylsalicylic acid. For the use of low-dose acetylsalicylic acid for cardiovascular indications, the addition of a vitamin C supplement is not required.

Salicylic acid: Salicylates inhibit active transport from the intestinal wall.

Isoprenaline: The chronotropic effect of isoprenaline decreases when given simultaneously with vitamin C.

Alcohol: Alcohol consumption lowers the levels of vitamin C in the blood. The effects of simultaneous use are unknown.

Mexiletine: When high doses of vitamin C and mexiletine are administered simultaneously, renal excretion of mexiletine may accelerate.

Barbiturates (Primidone): When given concurrently with barbiturates (primidone), urinary excretion of vitamin C may increase.

Amphetamine and tricyclic antidepressants: Vitamin C reduced renal tubular reabsorption of amphetamines and tricyclic antidepressants.

Flufenazin and other phenothiazines: Vitamin C has been reported to reduce the therapeutic effect of phenothiazines. The concentration of flufenazine may also decrease.

Corticosteroids: Corticosteroids increase vitamin C oxidation. However, it is not clinically significant.

Tetracyclines: Tetracyclines inhibit the intracellular metabolism of vitamin C and reabsorption at the level of kidney tubules.

Amygdalin: A case has been reported that the risk of cyanide poisoning increases as a result of simultaneous intake of high doses of vitamin C (>4000 mg) and amygdaline.

Aluminum: High doses of vitamin C taken together with aluminum can cause an increase in the reabsorption of aluminum. This interaction was not clinically significant in people with normal kidney function.

In theory; high doses of vitamin C can lead to acidification of urine, thereby unexpectedly undergone renal tubular reabsorption of acidic drugs, resulting in excessive response. On the other hand, basic drugs may show reduced reabsorption, resulting in a decrease in the therapeutic effect.

Interactions with Food/Supplements

Iron: Vitamin C can increase iron absorption in people with iron deficiency.
Small gradual increases in iron levels may be important in cases with hereditary hemochromatosis or because this disease may aggravate iron overload in heterozygous carriers.

Laboratory interactions

Since vitamin C is a powerful reducing agent (electron donor), it can cause chemical interaction in laboratory tests, including glucose, creatinine, carbamazepine, uric acid and inorganic phosphate analysis in urine and serum, and occult blood analysis in faeces. Using specific tests that do not depend on the reducing properties or cutting off the extra vitamin C taken with the diet will prevent unwanted interactions. See the manufacturer's information to determine if vitamin C interacts with the test.

Vitamin C can interact with tests that measure urine and blood glucose, causing erroneous readings, but has no effect on blood glucose levels. To determine if vitamin C is interacting and for guiding accuracy in reading, see the instructions for using the meter or test kit.

Vitamin C is an obstacle in the determination of serum transaminases and lactic dehydrogenase with an autoanalyzer. Occult blood and serum theophylline levels may affect some tests applied for determination.

4.6 Pregnancy and lactation

General advice
Pregnancy category: C

Women with childbearing potential/Contraception
Oral contraceptives reduce the level of endogenous serum of vitamin C. Vitamin C in a daily dosage of 1 gram can increase the bioavailability of ethinylestradiol from oral contraceptive preparations, which can increase adverse effects from ethinylestradiol. If ethinylestradiol is used simultaneously in the treatment with ascorbic acid, the patient should be monitored for the adverse effects of ethinylestradiol.

Pregnancy
Studies on animals are insufficient in terms of effects on pregnancy and/or birth and/or postnatal development (see section 5.3).
The potential risk for humans is unknown. ANTOKSİ-C should not be used during pregnancy unless deemed necessary by the physician.

Vitamin C is considered reliable during pregnancy when taken at the recommended dosage. However, since there are not enough controlled human studies evaluating the risk of vitamin C treatment during pregnancy, the product should only be used when recommended by the physician during pregnancy. The recommended dose should not be exceeded, since chronic overdose can be harmful to the fetus.

Lactation
Ascorbic acid passes into breast milk. It is not known whether taking high doses has a harmful effect on the baby, but it is theoretically possible. Therefore, it is recommended that breastfeeding mothers do not exceed the maximum daily requirement unless the expected benefit potential is more than the risk.

The reproductive capability/Fertility
There is no evidence that vitamin C at normal endogenous levels causes adverse reproductive effects in humans. It is not known whether it affects the reproductive ability.

4.7 Effects on ability to drive and use machines
ANTOKSİ-C has no effect on the ability to drive and use machines or has a negligible effect.

4.8 Undesirable effects

The evaluation of undesirable effects is done based on the following frequencies::
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) and unknown (estimation based on the existing data is impossible).

Following approval of product use, the following adverse reactions are described. Since these reactions are reported voluntarily, it is unlikely to reliably predict the frequency of events.

Blood and lymphatic system diseases
Very rare: Hemolysis in patients with G6PD (Glucose-6-phosphatase deficiency) when used above the recommended dose.

Immune system diseases
Very rare: Allergic reaction, anaphylactic reaction, anaphylactic shock. Hypersensitivity reactions that are rarely observed and determined by relevant laboratory findings and clinical symptoms:
- allergic asthma syndrome
- It includes reactions that affect mild to moderate skin, respiratory tract, gastrointestinal tract and cardiovascular system with symptoms such as rash, urticaria, allergic edema and angioedema, pruritus and cardio respiratory distress.

Nervous system disorders
Unknown: Headache, dizziness, fatigue, sleep disturbance

Gastrointestinal diseases
Very rare: Diarrhea, nausea, vomiting, abdominal pain, dyspepsia

Skin and subcutaneous tissue disorders
Unknown: Flushing (redness) or redness

Musculoskeletal and Connective Tissue Disorders
Rare: Sensitivity, pain, fever or swelling in the arms and legs.

Kidney and urinary disorders
Rare: Difficulty urinating
Unknown: Kidney stone formation in people with potential for hyperoxaluria, diuresis and kidney stones, or when used above the recommended dose

General disorders and diseases related to the application site
Unknown: Injection and infusion site reactions.

4.9. Overdose and therapy
There is no evidence that this product can cause overdose when used as recommended.
Vitamin C intake from all other sources should be considered.
Clinical findings and symptoms, laboratory findings and the consequences of overdose are highly variable, based on the individual's susceptibility and environmental conditions.
In the general picture of vitamin C overdose there is an increase in gastrointestinal disorders including diarrhea, nausea and vomiting.
If these symptoms occur, treatment should be discontinued and symptomatic treatment should be carried out.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Ascorbic acid (Vitamin C)
ATC code: A11GA

Vitamin C is a cofactor for various enzymes involved in collagen, carnitine and neurotransmitter biosynthesis; It is a water-soluble antioxidant and increases gastrointestinal absorption of non-nutritional iron. Due to the body's low capacity to store vitamin C, people need to take enough vitamin C regularly. While marginal deficiency results in fatigue, feeling unhealthy, impaired concentration, its severe deficiency leads to weakening of collagen structures, resulting in tooth loss, joint pain and connective tissue diseases (impaired bone growth and unbalanced ossification), delayed wound healing and worsening immunity.

Dehydroascorbic acid, vitamin C and its metabolite, forms a reversible redox system that participates in many enzymatic reactions and forms the basis of the vitamin C action spectrum. Vitamin C is the primary water-soluble antioxidant in human serum and plays a leading role in protecting it from damage due to exposure to toxins and environmental pollutants (e.g. smoking) as well as free radicals that occur during the normal metabolism of plasma lipids and nucleic acids. Vitamin C is the only endogenous antioxidant that can fully protect all lipid classes against detectable peroxidative damage.

Vitamin C works as a cofactor by transferring electrons to enzymes that provide reducing equivalents in a series of hydroxylation and amidation reactions.
The importance of vitamin C for the human body is most clearly manifested in clinically apparent vitamin C deficiency, that is, in scoreboard. Vitamin C plays an important role in the production of hydroxyproline, which is essential for the development of functionally active collagen. Symptoms such as delayed wound healing, bone growth disorders, vascular fragility and dentin formation diseases seen on the scoreboard are the result of impaired collagen formation.

Also, vitamin C concentrations in plasma and leukocytes quickly decrease in the event of infection and stress. Vitamin C, together with collagen synthesis and wound healing, which is important for cell-mediated immune responses such as leukocyte and macrophage functions, neutrophil motility, phagocytosis, antimicrobial activity, interferon synthesis, allergic reactions, and the skin's physical barrier against infections. is necessary. Vitamin C contributes to maintaining the redox integrity of the cells, thereby protecting them against reactive oxygen species that occur during a respiratory burst and inflammatory response. Vitamin C has antiviral properties. All these different properties of vitamin C contribute to the role of supporting immune functions. Increased vitamin C intake has been shown to benefit many groups at risk of infection and reduce the severity and duration of the common cold.

In summary, vitamin C (ascorbic acid) is an important water-soluble vitamin and antioxidant. Due to the body's low capacity to store vitamin C, people need to take enough vitamin C regularly.

5.2 Pharmacokinetic properties

General properties:

Absorption:

Vitamin C is absorbed mainly through the sodium-dependent active transport mechanism in the upper part of the small intestine. When vitamin C is present in high concentrations,

absorption occurs through passive diffusion. After oral administration of doses of 1-12 g, the absorbed ascorbic acid ratio drops from approximately 50% to 15%, but the amount of absorbed substance continues to increase.

Distribution:
The binding rate of ascorbic acid to plasma proteins is approximately 24%. Serum concentrations are normally 10 mg/L (60 μmol/L). Concentrations below 6 mg/L (35 μmol/L) indicate that vitamin C intake is not always at adequate levels. Concentrations below 4 mg/L (20 μmol/L) indicate that vitamin intake is inadequate. In clinical score, serum concentrations are below 2 mg/L (10 μmol/L).

Biotransformation:
Ascorbic acid is partially metabolised to oxalic acid via dehydroascorbic acid. However, ascorbic acid is excreted largely unchanged in urine and feces when taken in excessive amounts. Ascorbic acid-2-sulfate is also found in the urine as a metabolite.

Elimination:
Physiological body stores are approximately 1500 mg. The excretion half-life of ascorbic acid is related to the mode of administration, the amount administered, and the rate of absorption. After administration of 500 mg sodium ascorbate intravenously, its half-life is approximately 6 hours. The half-life after an oral dose of 1 g is about 13 hours. When taking 1-3 g of vitamin C per day, the main way of excretion is the kidneys. In doses exceeding 3 days, increased amounts are excreted unchanged with feces.

5.3 Preclinical safety data
Specific studies for this product have not been conducted. Preclinical data based on single and repeated dose toxicity, genotoxic, carcinogen potential, reproductive toxicity studies did not pose a specific risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Water for injection
Metyl paraben (E218)
Propyl paraben (E216)
Sodium hydroxide

6.2. Incompatibilities
This product should not be mixed with other drugs, as incompatibility studies are not available.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature under 25 ° C.

6.5. Nature and contents of container
Colorless type I glass ampoule.

6.6 Special precautions for and other handling
Unused products or waste materials must be disposed of in accordance with the "Regulation Related to the Control of Medical Wastes" and "Regulation Related to the Control of Packaging Materials and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER(S)
2020/15

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
First licence date: 24.01.2020
Licence revision date:

10. DATE OF REVISION OF THE TEXT

02.06.2020