SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: SERIOUS ADVERSE REACTIONS, INCLUDING TENDINIT AND TENDON RIPPING, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS, AND EXTENSION OF MYASTENIA GRAVIS

- Fluoroquinolones, including SIPROSAN, can cause disabling and irreversible adverse reactions such as:
    - o Tendonitis and tendon rupture
    - o Peripheral neuropathy
    - o Central nervous system effects

In patients in whom any of these reactions are observed, the use of SIPROSAN should be discontinued immediately and the use of fluoroquinolones should be avoided.

- Fluoroquinolones, including Siprosan, may exacerbate muscle weakness in patients with myasthenia gravis. The use of SIPROSAN should be avoided in patients with a known history of myasthenia gravis.
- Since fluoroquinolone group drugs, including SIPROSAN, are known to be associated with serious adverse reactions, they can be used in the following indications if there is no other alternative.
    - o Uncomplicated urinary infection
    - o Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT

SIPROSAN® 500 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

One film-coated tablet contains 582 mg ciprofloxacin hydrochloride monohydrate equivalent to 500 mg ciprofloxacin.

Excipients:

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

White, oblong film-coated tablet

4. CLINICAL PROPERTIES

4.1 Therapeutic indications

Fluoroquinolones, including Siprosan, should not be used in acute bacterial exacerbation of chronic bronchitis and in the presence of alternative treatment options in uncomplicated urinary infections due to the risk of serious side effects. In addition, susceptibility must be proven with an antibiogram in urinary infections.

It can be used in these indications when other treatment options have failed.

Official guidelines on the correct use of antibacterial drugs should be observed.

SIPROSAN should only be used in the treatment of infections proven or suspected to be caused by susceptible bacteria.

SIPROSAN 500 mg film-coated tablet is indicated for the treatment of the following indications (See Sections 4.4 and 5.1).

Special attention should be paid to available information regarding resistance to ciprofloxacin before initiating therapy. Official guidelines on the appropriate use of antibacterial agents should be considered.

Adults:

- Lower respiratory tract infections due to Gram-negative bacteria
  - Exacerbations of chronic obstructive pulmonary disease (see section 4.4)
  - Broncho-pulmonary infections in cystic fibrosis or bronchiectasis
  - Pneumonia
- Chronic suppurative otitis media (See Section 4.4)
  - Acute exacerbations of chronic sinusitis, especially when due to Gram-negative bacteria (see section 4.4)
- Urinary tract infections
  - Uncomplicated urinary tract infections (See section 4.4)
  - Complicated urinary tract infections
  - pyelonephritis
- Genital tract infections
  - Gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
  - Epididymo-orchitis, including cases due to susceptible *Neisseria gonorrhoeae*

- Pelvic inflammatory disease, including cases due to susceptible *Neisseria gonorrhoeae*
- Prostatitis

- Gastrointestinal tract infections (eg, traveler's diarrhea)İntra-abdominal enfeksiyonlar
- Skin and soft tissue infections caused by Gram-negative bacteria
- Malignant otitis externa (See Section 4.4)
- Bone and joint infections
- Prophylaxis of invasive infections due to *Neisseria meningitidis* over 18 years of age
- Respiratory anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin can also be used in combination therapy in the treatment of patients with neutropenic fever thought to be caused by bacterial infection.

Children and adolescents:

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa* (range of clinical studies: 5-17 years)
- Complicated urinary tract infections and pyelonephritis, when other alternatives are not suitable in case of sensitivity to the agent, (age range where clinical studies were performed: 1-17 years)
- Respiratory anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin can also be used for the treatment of severe infections in children and adolescents when other agents cannot be used if deemed necessary.

Treatment should only be initiated by physicians experienced in the management of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology:

Dosage is determined by the indication, the severity and location of the infection, the susceptibility of causative organisms to ciprofloxacin, the renal function of the patients, and body weight in children and adolescents.

The duration of treatment is based on the severity of the disease and the clinical and

bacteriological course.

In the treatment of infections caused by certain bacteria (eg *Pseudomonas aeruginosa*, Acinetobacter or Staphylococci), higher doses of ciprofloxacin and co-administration with other suitable antibacterial agents may be necessary.

Treatment of some infections (eg, pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients, and bone and joint infections) may also require co-administration with other appropriate antibacterial agents, depending on the pathogens involved.

Adults

Indications		**daily dose in mg**	**Total duration of treatment (potentially including initial parenteral therapy with ciprofloxacin)**
Lower respiratory tract infections - Bronchopulmonary infections in cystic fibrosis or bronchiectasis - Pneumonia (See Section 4.4)		500mg to 750mg twice daily	7 to 14 days
Urinary tract infections (See Section 4.4)	Complicated urinary tract infections	500mg twice daily	7 days
	Pyelonephritis	500mg to 750mg twice daily	At least 10 days, in some specific cases (such as abscess) may be continued for more than 21 days
Genital tract infections	Gonococcal urethritis and cervicitis	500mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory disease	500mg to 750mg twice daily	At least 14 days
	Prostatitis	500mg to 750mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Gastrointestinal tract infections and intra-	Empirical treatment of diarrhea and		

abdominal infections	severe traveler's diarrhea caused by bacterial pathogens, including *Shigella* species other than *Shigella dysenteriae* type 1.	500mg twice daily	1 day
	Diarrhea caused by *Shigella dysenteriae* type 1	500mg twice daily	5 days
	Diarrhea caused by *Vibrio cholerae*	500mg twice daily	3 days
	Typhoid fever	500mg twice daily	7 days
	Intra-abdominal infections caused by Gram-negative bacteria	500mg to 750mg twice daily	5 to 14 days
Skin and soft tissue infections		500mg to 750mg twice daily	7 to 14 days
Bone and joint infections		500mg to 750mg twice daily	3 months maximum
Febrile neutropenic diseases thought to be caused by bacterial infection Ciprofloxacin should be administered with appropriate antibacterial agents in accordance with official guidelines.		500mg to 750mg twice daily	Treatment should be continued throughout the entire period of neutropenia.
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500mg as a single dose	1 day (single dose)
Post-exposure prophylaxis and curative therapy for individuals who can receive oral therapy when clinically appropriate. Administration of the drug should be initiated as soon as possible after suspected or confirmed exposure.		500mg twice daily	60 days from confirmation of exposure to *Bacillus anthracis*

Application frequency and duration:

See. Section 4.2.

Method of Application:

It is administered orally. The tablets are swallowed whole with some liquid.

It can be taken regardless of meal times. The active substance is absorbed faster when taken on an empty stomach. In this case, the tablets should not be taken with dairy products or mineral fortified beverages (eg milk, yoghurt, calcium-fortified orange juice) (see section 4.5).

It is recommended to administer ciprofloxacin in intravenous form to patients who cannot take tablets due to the severity of the disease or for other reasons (eg, if the patient is receiving enteral nutrition). After intravenous administration, treatment can be continued orally.

Additional information on special populations:

Kidney failure:

Recommended initial and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min./1,73 m²]	**Serum Creatinine [µmol/L]**	**Oral Dose [mg]**
>60	<124	See. General Dose.
30-60	124 ila 168	250-500mg every 12 hours
<30	>169	250-500mg every 24 hours
Patients receiving hemodialysis treatment	>169	250-500 mg every 24 hours (post dialysis)
Patients receiving peritoneal dialysis treatment	>169	250-500mg every 24 hours

Dosage studies have not been conducted in children with renal impairment.

Liver failure:

No dosage adjustment is necessary in patients with impaired hepatic function.

Dosage studies have not been conducted in children with hepatic impairment.

Pediatric population:

Indications	**daily dose in mg**	**Total treatment duration (potentially including first**

		parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose	10 to 21 days
Post-exposure prophylaxis and curative therapy for individuals who can receive oral therapy when clinically appropriate. Administration of the drug should be initiated as soon as possible after suspected or confirmed exposure.	10 mg/kg to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose	60 days from confirmation of exposure to *Bacillus anthracis*
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose	By type of infection

Geriatric population:

Elderly patients should receive a dose selected based on the severity of the infection and the patient's creatinine clearance.

4.3 Contraindications

- Hypersensitivity to ciprofloxacin or other quinolones or to any component of the product (see section 6.1).
- Concomitant use of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Serious potentially irreversible and disabling adverse reactions including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects

Fluoroquinolones, including SIPROSAN, have been associated with serious adverse reactions that can cause disability and are potentially irreversible. Common adverse reactions musculoskeletal and peripheral nervous system (such as tendinitis, tendon rupture, swelling or inflammation of tendons, tingling or numbness, numbness of limbs, myalgia, muscle weakness,

arthralgia, swelling of joints) arthralgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidality, insomnia, severe headache and confusion) (See Section 4.8).

These reactions may occur within hours or weeks after starting SIPROSAN. Patients of all age groups or without pre-existing risk factors have experienced these adverse reactions.

SIPROSAN should be discontinued immediately at the first signs or symptoms of any serious adverse reaction. In addition, the use of fluoroquinolones, including SIPROSAN, should be avoided in patients experiencing any of these serious adverse reactions in association with fluoroquinolones.

Acute bacterial exacerbation of chronic bronchitis, acute exacerbations of chronic sinusitis, chronic suppurative otitis media, malignant otitis externa and uncomplicated urinary tract infections

It can be used in cases of acute bacterial exacerbation of chronic bronchitis, acute exacerbations of chronic sinusitis, chronic suppurative otitis media, malignant otitis externa and uncomplicated urinary infections where other treatment options have failed. In addition to this, susceptibility should be proven by antibiogram in urinary infections.

Indications		**daily dose in mg**	**Total treatment duration (potentially including first parenteral treatment with ciprofloxacin)**
Lower respiratory tract infections - exacerbations of chronic obstructive pulmonary disease		500mg to 750mg twice daily	7 to 14 days
Upper respiratory tract infections	Acute exacerbations of chronic sinusitis	500mg to 750mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500mg to 750mg twice daily	7 to 14 days
	Malignant otitis externa	750 mg twice daily	28 days to 3 months
Uncomplicated urinary tract infections		250mg to 500mg twice daily	3 days
		A single dose of 500 mg can be used in pre-menopausal	

	women.

Severe Infections and/or severe infections due to gram positive or anaerobic bacteria
Ciprofloxacin monotherapy is not suitable for the treatment of severe infections and infections caused by Gram-positive or anaerobic pathogens. In such infections, SIPROSAN should be administered together with other suitable antibacterial agents.

Streptococcal Infections (including *Streptococcus pneumoniae*)
SIPROSAN is not recommended for the treatment of streptococcal infections due to its insufficient efficacy.

Genital tract infections
Gonococcal urethritis, cervicitis, epididymo-orchitis, and pelvic inflammatory diseases may result from fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. Therefore, SIPROSAN should be administered in the treatment of gonococcal urethritis or cervicitis only when ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should be considered in combination with another appropriate antibacterial agent (eg, a cephalosporin) only if ciprofloxacin-resistant *Neisseria gonorrhoeae* cannot be excluded. If clinical improvement is not achieved after three days of treatment, the treatment should be re-evaluated.

Urinary tract infections
The resistance of *Escherichia coli,* which is the most common associated pathogen in urinary tract infections, to fluoroquinolones varies according to the region of residence. It is recommended that prescribing physicians locally consider the prevalence of resistance to fluoroquinolones by *Escherichia coli* in their area.

A single dose of SIPROSAN, which can be used for uncomplicated urinary tract infections in pre-menopausal women, is expected to be associated with lower efficacy rather than longer treatment duration. This should be given further consideration in terms of the increasing level of resistance of *Escherichia coli* to quinolones.

Intra-abdominal infections
There are limited data on the efficacy of SIPROSAN in post-surgical intra-abdominal

infections.

Travel diarrhea
Information on resistance to ciprofloxacin in relevant pathogens in countries of travel should be considered.

Bone and joint infections
SIPROSAN should be used in combination with other antimicrobial agents depending on the microbiological results.

Respiratory tract anthrax
Use in humans is based on *in-vitro* susceptibility data and experimental data from animals with limited data in humans. Treating physicians should consult national and/or international consensus documents on the treatment of anthrax.

Children and adolescents
Use of ciprofloxacin in children and adolescents should follow current official guidelines. Ciprofloxacin therapy should only be initiated by physicians experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy on the weight-bearing joints of immature animals. Safety data (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) from a randomized, double-blind study of ciprofloxacin use in children revealed an incidence of suspected drug-related arthropathy (different from clinical signs and symptoms of the joint) at +42 days of 7.2% to 4.6%. The incidence of drug-related arthropathy at one-year follow-up was 9% and 5.7%, respectively. The increase in suspected drug-related arthropathy cases over time was not statistically significant between the groups. Because of possible joint and/or surrounding tissue adverse events, treatment should only be initiated after a careful benefit/risk assessment (see section 4.8).

Broncho-pulmonary infections in cystic fibrosis
Children and adolescents aged 5 to 17 years were included in clinical trials. There is more limited experience in the treatment of children aged 1 year to 5 years.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin therapy for urinary tract infections should be considered when other treatments are unavailable and should be based on microbiological results. Children and adolescents aged 1 to 17 years were included in clinical trials.

Other specific severe infections
It can be used in other severe infections in accordance with official guidelines or after careful benefit-risk assessment when other treatments cannot be used, or after conventional treatment has failed, and when microbiological documentation can justify the use of Siprosan.

The use of SIPROSAN for specific severe infections other than those mentioned above has not been evaluated in clinical studies and clinical experience is limited. Therefore, care should be taken when treating patients with these infections.

Hypersensitivity
In some cases, hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur immediately after the first administration (see section 4.8) and may be life-threatening.

In such cases, SIPROSAN should be discontinued and appropriate medical treatment should be applied.

musculoskeletal system
SIPROSAN should not be used in patients with a history of tendon disease/disorder generally related to quinolone therapy. However, in very rare cases, after evaluation of the microbiological documentation of the causative organism and the risk/benefit balance, SIPROSAN may be prescribed to these patients for the treatment of some severe infections, particularly when standard therapy has failed or bacterial resistance is present, where microbiological data can justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), which can sometimes be bilateral, may occur with SIPROSAN, even within the first 48 hours of treatment. Tendon inflammation and rupture can occur up to several months after ciprofloxacin treatment is discontinued. This risk of tendinopathy may be increased in elderly patients or patients

treated concomitantly with corticosteroids (see section 4.8).

Ciprofloxacin therapy should be discontinued if any sign of tendinitis appears (eg painful swelling, inflammation). Care should be taken to rest the affected leg.

Exacerbation of Myasthenia Gravis:
Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing reported serious adverse events, including the need for ventilatory support and death, in patients with myasthenia gravis using fluoroquinolones have been associated with fluoroquinolones. Patients with a history of myasthenia gravis should avoid the use of fluoroquinolones. (See Section 4.8).

Visual disturbances
If visual impairment begins or any effects are felt on the eyes, an ophthalmologist should be consulted immediately.

Cardiac disorders
May increase the risk of long QT syndrome or Torsades de Pointes when used with drugs that can cause long QT syndrome/Torsades de Pointes. Therefore, it should not be used together with such drugs.

Caution should be exercised when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors that may prolong the QT interval. For example;
• Congenital long QT syndrome
• Concomitant use of drugs that may prolong the QT interval (eg concurrent use class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
• Uncorrected electrolyte imbalance (eg, hypokalemia, hypomagnesemia)
• Cardiac diseases (eg heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc prolonging drugs. Therefore, caution should be exercised when using fluoroquinolones, including ciprofloxacin, in this population (See Sections 4.2, 4.5, 4.8, 4.9).

Hypoglycemia

As with other quinolones, hypoglycemia has been most commonly reported in diabetic patients, particularly in the elderly population. Careful monitoring of blood glucose is recommended in all diabetic patients (see section 4.8).

Gastrointestinal tract

The occurrence of severe and persistent diarrhea during or after treatment (including for several weeks after treatment) may indicate antibiotic-associated colitis (a life-threatening condition with potentially fatal consequences) requiring emergency treatment (see section 4.8). In such cases, SIPROSAN should be discontinued immediately and appropriate treatment should be initiated. In this case, anti-peristaltic drugs are contraindicated.

Photosensitivity

Ciprofloxacin has been shown to cause photosensitivity reactions. Therefore, patients taking SIPROSAN should not be exposed to intense sunlight or UV rays (See Section 4.8).

Central nervous system (CNS)

As with other quinolones, SIPROSAN is known to trigger seizures or lower the seizure threshold.

Cases of status epilepticus have been reported. SIPROSAN should be used with caution in patients with a predisposition to seizures and central nervous system disorders. In case of seizure, SIPROSAN should be discontinued (See Section 4.8).

Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychotic reactions may lead to suicidal ideation/thoughts and suicide attempt or suicide. If the patient develops any of these reactions, SIPROSAN should be discontinued.

Cases of sensory or sensorimotor polyneuropathy resulting in paresthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving ciprofloxacin. In order to prevent the development of irreversible conditions, SIPROSAN treatment should be discontinued in patients with symptoms of neuropathy, including pain, burning, tingling, numbness and/or weakness. (See Section 4.8).

Renal and urinary system

Crystalluria associated with the use of ciprofloxacin has been reported (see section 4.8). Patients taking ciprofloxacin should drink plenty of water and avoid excessive alkalinity of the urine.

Kidney dysfunction

Since SIPROSAN is largely excreted by the kidneys, dose adjustment is required in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin (see section 4.2).

Dose adjustment should be considered in elderly patients, since renal function is reduced. Consideration should be given to dose reduction when renal and hepatic dysfunction are present together.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). If any signs or symptoms of liver disease (anorexia, jaundice, dark urine, itching or tender abdomen) are present, treatment should be discontinued (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency

Hemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. The use of ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, the possible occurrence of hemolysis should be monitored.

Resistance

During or following ciprofloxacin therapy, bacteria resistant to ciprofloxacin may be isolated, with or without clinically significant superinfection. Choosing ciprofloxacin during long-term treatments and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* may pose a different risk for bacteria resistant to ciprofloxacin..

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and may therefore lead to increased serum concentration of co-administered substances metabolised by this enzyme (eg theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin with

tizanidine is contraindicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be closely monitored for clinical signs of overdose and serum concentrations (eg theophylline) may need to be determined. (See Section 4.5).

Methotrexate

Concomitant use of ciprofloxacin and methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* may result in false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interactions with other medicinal products and other forms of interaction

Effect of other medicinal products on ciprofloxacin

Drugs known to prolong the QT interval

Similar to other fluoroquinolones, Siprosan should be used with caution in patients taking drugs known to prolong the QT interval (eg Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation complex formulations

The absorption of ciprofloxacin decreases when iron, sucralfate or antacids, strongly buffered drugs (antiretroviral drugs), therapeutic products containing magnesium, aluminum or calcium, and polymeric phosphate binders such as sevelamer and lanthanum carbonate are taken with oral SIPROSAN. When concomitant use is necessary, SIPROSAN should be given 1-2 hours before or at least 4 hours after other drugs. This limitation does not apply to H2 receptor blocker class antacid drugs.

Food and dairy products

Calcium taken during meals does not significantly affect the absorption of ciprofloxacin. However, concomitant use of ciprofloxacin and dairy products or beverages with mineral additives (eg milk, yoghurt, calcium-fortified orange juice) may reduce the absorption of ciprofloxacin. Therefore, such use of SIPROSAN should be avoided.

Probenecid

Probenecid inhibits the renal excretion of ciprofloxacin. Concomitant use with therapeutic products containing probenecid leads to increased serum concentrations of ciprofloxacin.

Metoclopramide

Metoclopramide accelerates the absorption of (oral) ciprofloxacin and causes it to reach peak blood level in a shorter time. However, it has no effect on the bioavailability of ciprofloxacin.

Omeprazole

Co-administration of ciprofloxacin with therapeutic products containing omeprazole may result in a slight decrease in Cmax and AUC of ciprofloxacin.

Effect of ciprofloxacin on other medicinal products

Tizanidine

Therapeutic products containing tizanidine should not be administered together with SIPROSAN. (See Section 4.3). In a clinical study in healthy subjects, an increase in serum concentrations of tizanidine was seen (Cmax increase: 7-fold, range: 4-21-fold, AUC increase: 10-fold, range: 6-24-fold) when co-administered with ciprofloxacin. Hypotensive and sedative effects are increased due to increased serum concentrations (see section 4.4).

Methotrexate

Concomitant administration of SIPROSAN and methotrexate may inhibit the transport of methotrexate from the renal tubules, resulting in increased plasma levels of methotrexate. This may increase the risk of toxic reactions associated with methotrexate. Concomitant use of ciprofloxacin and methotrexate is not recommended (see section 4.4).

Theophylline

Concomitant administration of ciprofloxacin and therapeutic products containing theophylline may lead to an undesirable increase in serum theophylline levels. In this case, undesirable effects of theophylline may occur, and rarely these effects can be life-threatening or fatal. If the use of two therapeutic products in combination is necessary, the serum theophylline level should be monitored and the theophylline dose should be reduced accordingly. (See Section 4.4).

Other xanthine derivatives

When ciprofloxacin and products containing caffeine or pentoxifylline (oxpentifylline) are used concomitantly, increased serum concentrations of these xanthine derivatives have been reported.

Cyclosporine

Transient increases in serum creatinine have been observed when therapeutic products containing ciprofloxacin and cyclosporine are given concomitantly. Therefore, serum creatinine levels of these patients should be checked frequently (twice a week).

Vitamin K antagonists

Concomitant administration of SIPROSAN with a vitamin K antagonist may increase the anticoagulant effects of these drugs. This risk may vary depending on the underlying infection, the age and general condition of the patient, so it is difficult to determine the contribution of ciprofloxacin to the increase in INR (international normalized ratio). INR should be monitored frequently during or immediately after administration of SIPROSAN with a vitamin K antagonist (eg, warfarin, acenocoumarol, phenprocoumon or fluindione).

Duloxetine

Clinical studies have shown that concomitant use of duloxetine with potent CYP450 1A2 isoenzyme inhibitors such as fluvoxamine may result in increased AUC and Cmax of duloxetine. Although there are no clinical data on a possible interaction with ciprofloxacin, similar effects can be expected with concomitant use. (See Section 4.4).

Ropinirole

In a clinical study, concomitant use of ropinirole, a moderate inhibitor of CYP450 1A2 isozyme, and ciprofloxacin resulted in increases in Cmax and AUC of ropinirole by 60% and 84%, respectively. When co-administered with SIPROSAN, monitoring for ropinirole-related undesirable effects and dose adjustment is recommended (see section 4.4).

Lidocaine

Concomitant use of lidocaine-containing therapeutic products with the CYP450 1A2 isozyme inhibitor, ciprofloxacin, has been shown to reduce intravenous lidocaine clearance by 22% in healthy volunteers. Although lidocaine therapy is well tolerated, possible side effects related to ciprofloxacin that may occur with concomitant administration are reported in case reports.

clozapine

Following co-administration of 250 mg of ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine increased by 29% and 31%, respectively. Clinical monitoring and appropriate clozapine dose adjustment are recommended during or immediately after concomitant use with SIPROSAN (see section 4.4).

sildenafil

Sildenafil Cmax and AUC were approximately doubled in healthy subjects following a 50 mg oral dose co-administered with 500 mg ciprofloxacin. Therefore, the risks and benefits should be considered when SIPROSAN is prescribed together with sildenafil.

phenytoin

Changes (increase or decrease) in serum phenytoin levels have been observed in patients receiving ciprofloxacin and phenytoin simultaneously. In this case, monitoring of drug levels is recommended.

Agomelatine

In clinical studies, fluvoxamine, a potent CYP450 1A2 isoenzyme inhibitor, has been shown to significantly inhibit agglomelatine metabolism, increasing the exposure to agomelatine 60-fold. Although there are no clinical data for a similar interaction with ciprofloxacin, a moderate CYP450 1A2 inhibitor, similar effects can be expected with concomitant use (see section 4.4).

Zolpidem

Co-administration with ciprofloxacin may increase zolpidem blood levels, concomitant use is not recommended.

Additional information on special populations

Pediatric population:

No interaction studies have been conducted in the pediatric population.

4.6 Pregnancy and lactation

General Advice

Pregnancy category: C

Women of childbearing potential / Contraception

There are no adequate data from the use of ciprofloxacin in women of childbearing potential. As a precaution, it is recommended to use an appropriate method of contraception.

Pregnancy period

Data from the use of ciprofloxacin in pregnant women do not indicate malformations or fetal/neonatal toxicity. Since effects on immature cartilage have been observed in juvenile and prenatal animals exposed to quinolones, it cannot be excluded that the drug may cause articular cartilage damage in the immature human organism/fetus (see section 5.3).

As a precaution, the use of ciprofloxacin should be avoided during pregnancy.

Lactation period

Ciprofloxacin is excreted into breast milk. Due to the possible risk of articular damage, ciprofloxacin SIPROSAN is not recommended for use during breastfeeding (see section 5.3).

Reproductive ability/Fertility

For studies on animals, see Section 5.3.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Therefore, it can cause a decrease in the ability to drive or drive.

4.8 Undesirable effects

Adverse drug reactions based on all clinical studies with ciprofloxacin (oral, parenteral) are listed by CIOMS III category for frequency (total n=51621).

The frequency of adverse reactions reported in the use of SIPROSAN is summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing severity. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥ 1/1.000 to < l/100); rare (≥1/10.000 to <1/1.000); very rare (< l/10.000), unkonwn (could not be estimated from the available data).

Adverse reactions that were identified only during post-marketing surveillance and whose

frequency cannot be estimated are listed under the heading “unknown”.

System Organ Class	Comm on	Uncommon	Rare	Very Rare	Unknown
Infections and infestations		Mycotic superinfection s			
Blood and lymphatic system diseases		Eosinophilia	leukopenia, anemia, neutropenia, leukocytosis, thrombocytope nia, thrombocythe mia	Hemolytic anemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)	
Immune system diseases			Allergic reaction, allergic edema / angioedema	anaphylactic reaction, anaphylactic shock (life threatening) (see section 4.4), serum sickness-like reaction	
Metabolism and nutrition system diseases		Decreased appetite and food intake	hyperglycemia Hypoglycemia (See Section 4.4)		
Psikiyatrik hastalıklar		Psychomotor hyperactivity/ agitation	confusion and disorientation, anxiety reactions, abnormal dreams (nightmares), depression (suicidal ideation/thoug hts or suicidal ideation and likelihood of committing suicide) (see section 4.4), hallucinations	psychotic reactions (suicidal ideation/thoughts or suicidal attempt and likelihood of committing suicide) (See Section 4.4)	Mania, including hypomani a
nervous system diseases		Headache, dizziness, sleep disturbances,	Paresthesia, dysesthesia, hypoesthesia, tremor	Migraine coordination disorder, gait difficulty,	peripheral neuropath y and Polyneuro

		taste disorders	(tremor), seizures (status epilepticus) (See Section 4.4), vertigo	olfactory disorders, intracranial hypertension (pseudotumor cerebri),	pathy (See Section 4.4)
Eye diseases			Visual disturbances (eg diplopia)	Visual discolorations	
Ear and inner ear diseases			tinnitus, hearing loss/hearing reduction		
cardiac diseases			tachycardia		Ventricular arrhythmia, torsades de pointes (especially in patients with risk factors for QT prolongation), prolonged QT on ECG (See Sections 4.4 and 4.9)
Vascular diseases			Vasodilation, hypotension, syncope	vasculitis	
Thoracic and mediastinal disorders			Dyspnea (including asthma-related conditions)		
Gastrointestinal diseases	Nausea, diarrhea	Vomiting, gastrointestinal and abdominal pain, dyspepsia, flatulence	Antibiotic-induced colitis (very rarely fatal)	pancreatitis	

Hepatobiliary diseases		Increased transaminase levels, increased bilirubin	Hepatic failure, cholestatic jaundice, hepatitis	Liver necrosis (very rarely, may progress to life-threatening hepatic failure.) (See section 4.4)	
Skin and subcutaneous tissue diseases		Rash, itching, urticaria	Photosensitivity reactions, (See Section 4.4)	petechiae, erythema, multiforme, erythema nodosum, Stevens-Johnson Syndrome (potentially life-threatening) , toxic epidermal necrolysis (potentially life-threatening)	Acute generalized exanthema-tious pustulosis (AGEP), Drug syndrome with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue and bone diseases		Musculoskeletal pain (eg extremity pain, back pain, chest pain) Arthralgia (joint pain)	Myalgia, arthritis, increased muscle tone and cramping	Muscle weakness, tendinitis, tendon rupture (mostly Achilles tendon) (see section 4.4), exacerbation of myasthenia gravis (see section 4.4)	
Kidney and urinary tract diseases		renal disorder	renal failure hematuria Crystalluria (See Section 4.4) tubulointerstitial nephritis		
General disorders and administration site conditions		Asthenia, Fever	edema, sweating (hyperhidrosis)		
Studies		Increase in alkaline phosphatase	Amylase increase		INR (International normalized ratio) increase (in

					patients treated with vitamin K antagonists)

* These reactions are adverse reactions from post-marketing studies and generally from patients with risk factors for QT prolongation (see section 4.4).

Pediatric patients
The incidence of arthropathy (arthralgia, arthritis) mentioned above refers to data from studies for adults. Arthropathy commonly occurs in children (see section 4.4).

4.9 Overdose and its treatment

An overdose of 12 g has been reported to cause mild symptoms of toxicity. Acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose include dizziness, tremor, headache, fatigue, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment, as well as crystalluria and hematuria. Reversible renal toxicity has been reported.

Apart from routine emergency actions and emergency measures such as medical carbon administration, it is recommended to monitor renal function, including urine pH and acidity, if necessary, to prevent crystalluria. The patient should be given plenty of fluids.

Antacids containing calcium or magnesium may reduce the absorption of ciprofloxacin in excessive doses.

Only small amounts (< 10%) of ciprofloxacin are eliminated by hemodialysis or peritoneal dialysis. In case of overdose, symptomatic treatment should be applied. ECG monitoring should be performed due to the possibility of prolongation of the QT interval.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemically used antibacterials, Fluoroquinolones
ATC code: J01MA02

Effect Mechanism

As a fluoroquinolone antibacterial drug, the bactericidal property of ciprofloxacin includes inhibition of type II topoisomerase (DNA gyrase) and topoisomerase IV, which are enzymes required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetic/pharmacodynamic relationship

Efficacy is mostly based on the relationship between the maximum serum concentration (Cmax) and minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relationship between the area under the curve (AUC) and MIC.

Resistance Mechanism

In vitro resistance to ciprofloxacin is commonly due to target site mutations in topoisomerase IV and DNA gyrase through multistep mutations. Cross-resistance results are variable between ciprofloxacin and other fluoroquinolones. Single mutations may result in reduced susceptibility rather than clinical resistance, but multiple mutations often result in cross-resistance between clinical ciprofloxacin resistance and the quinolone class.

Depending on the physicochemical properties of various active substances in the same class and the affinity of the transport systems of each active substance, the permeability and/or drug overflow pump resistance mechanisms may have variable effects on the susceptibility of fluoroquinolones. All *in-vitro* resistance mechanisms are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics, such as permeability barriers (common in *Pseudomonas aeruginosa*), and overflow mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by the Qnr gene has been reported.

<u>Antibacterial spectrum of activity</u>

Minimum concentration levels (breakpoints) indicating that the bacteria are susceptible or resistant distinguish susceptible strains from moderately susceptible strains and moderately susceptible from resistant strains:

EUCAST recommendations

Mikroorganizmalar	Sensitive	Resistant
Enterobacteriaceae	sensitive ≤ 0,5 mg/L	resistant > 1 mg/L
Pseudomonas species	sensitive ≤ 0,5 mg/L	resistant > 1 mg/L
Acinetobacter species	sensitive ≤ 1 mg/L	resistant > 1 mg/L
Staphylococcus species [1]	sensitive ≤ 1 mg/L	resistant > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	sensitive ≤ 0,5 mg/L	resistant > 0,5 mg/L
Neisseria gonorrhoeae	sensitive ≤ 0,03 mg/L	resistant > 0,06 mg/L
Neisseria meningitidis	sensitive ≤ 0,03 mg/L	resistant > 0,06 mg/L
Non-species breakpoints *	Sensitive ≤ 0,5 mg/L	resistant > 1 mg/L

1 *Staphylococcus* species - breakpoints for ciprofloxacin on high-dose therapy.

* In general, non-species-related breakpoints were identified based on PK/FD data and are independent of MIC distributions of specific species.

The prevalence of acquired resistance can vary geographically and over time, particularly in the treatment of serious infections, local information on resistance is desirable for certain species. If necessary, expert opinion may be sought in cases where the use of the agent for at least some types of infection is questioned and the local prevalence of resistance is increasing.

The following bacterial genera and strains have been shown to be commonly susceptible to ciprofloxacin:

Aerobic Gram-positive microorganisms

Bacillus anthracis (1)

Aerobic Gram-negative microorganisms

Aeromonas spp.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducrevi
*Moraxella catarrhalis**
Neisseria meningitidis
Pasteurella spp.
*Salmonella spp. **
*Shigella spp.**

*Haemophilius influenzae** *Vibrio spp.*
Legionella spp. *Yersinia pestis*

Anaerobic microorganisms
Mobiluncus

Other Microorganisms
Chlamydia trachomatis ($)
Chlamydia pneumoniae ($)
Mycoplasma hominis ($)
Mycoplasma pneumoniae ($)

Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Enterococcus faecalis ($)
Staphylococcus spp. (2)*

Aerobic Gram-negative microorganisms
Acinetobacter baumanni+ *Klebsiella pneumoniae**
*Burkholderia cepacia+** *Morganella morganii**
*Camplybacter spp. +** *Neisseria gonorrhoeae**
*Citrobacter freundii** *Proteus mirabilis**
Enterobacter aerogenes *Proteus vulgaris**
*Enterobacter cloacae** *Providencia spp.*
*Escherichia coli** *Pseudomonas aeruginosa**
Klebsiella oxytoca *Pseudomonas fluorescens*
*Serratia marcescens**

anaerobic microorganisms
Peptostreptococcus spp.
Propionibacterium acnes

The following microorganisms are considered resistant to ciprofloxacin by nature:
Aerobic Gram-positive microorganisms

Actinomyces
Enterococcus faecium
Listeria monocytogenes

Aerobic Gram-negative microorganisms
Stenotrophomonas maltophilia

anaerobic microorganisms
Except for those listed above

Other microorganisms
Mycoplasma genitalium
Ureaplasma urealitycum

* Clinical efficacy demonstrated in approved clinical conditions for susceptible isolates
+ Resistance rate ≥ 50% in one or more EU countries
($): Natural intermediate susceptibility in the absence of an acquired mechanism of resistance
(1): Studies have been conducted in experimental animal infections due to inhalation of *Bacillus anthracis* spores; In these studies, it was revealed that antibiotics started shortly after exposure prevented the disease from occurring if the treatment was done to reduce the number of spores in the organism under infective dose. Recommended use in human volunteers is based primarily on in vitro susceptibility and experimental animal data with limited human data. A two-month treatment period with 500 mg oral ciprofloxacin twice daily in adults has been considered the effective dose for the prevention of anthrax infection in humans. The treating physician should refer to national and/or international consensus documents for anthrax treatment.
(2): Methicillin-resistant *S. aureus* very commonly shows equiresistance to fluoroquinolones. Methicillin resistance rate is around 20% to 50% among all staphylococcal species and is generally higher in nosocomial isolates.

5.2 Pharmacokinetic properties

General features

Absorbation:

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg ciprofloxacin tablets, ciprofloxacin is rapidly and extensively absorbed, mostly from the small intestine, with

maximum serum concentrations reaching after 1-2 hours.
Single doses of 100-750 mg provide a dose-dependent maximum serum concentration (Cmax) of between 0.56 and 3.7 mg/l. The serum concentration increases proportionally at doses up to 1000 mg. Absolute bioavailability is about 70-80%.
An oral dose of 500 mg every 12 hours has been shown to provide an area under the serum concentration-time curve (AUC) level equivalent to that achieved by an intravenous infusion of 400 mg of ciprofloxacin given over 60 minutes every 12 hours.

Distribution:
The protein binding level of ciprofloxacin is low (20-30%). Ciprofloxacin is usually found in plasma in non-ionized form and has a large steady-state volume of distribution of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in various tissues such as the lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinus, inflammatory lesions (cantarian-derived blistering fluid) and the urogenital system (urine, prostate, endometrium); where the total concentration exceeds the plasma concentration.

Biotransformation:
Four metabolites identified as decetethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4) were detected at low concentrations. These metabolites show antimicrobial activity in vitro, albeit to a lesser degree than the parent compound.
Ciprofloxacin is known to be a moderate inhibitor of CYP 450 1A2 isoenzymes.

Elimination:
Ciprofloxacin is excreted mainly by the kidneys and to a lesser extent by the faeces. The serum elimination half-life in volunteers with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	oral administration	
	Pee	**feces**
Ciprofloxacin	44,7	25
Metabolites (M1-M4)	11,3	7,5

Renal clearance is between 180-300 mL/kg/hr and total body clearance is between 480-600

mL/kg/hr. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.
Severe deterioration in renal function leads to an increase in the half-life of ciprofloxacin to 12 hours.
Non-renal clearance of ciprofloxacin generally occurs via active trans-intestinal and metabolism. 1% of the dose is excreted by the biliary route. Ciprofloxacin is found in high concentrations in bile.

pediatric patients
Pharmacokinetic data in pediatric patients are limited.

In a study in children, Cmax and AUC were not dependent on age (over one year). No significant increase in Cmax and AUC was observed after multiple dosing (10 mg/kg three times daily).

In 10 children with severe sepsis, the Cmax value after 1 hour intravenous infusion of 10 mg/kg in children younger than 1 year was 6.1 mg/ml (range 4.6-8.3 mg/l) , while it was 7.2 mg/l (range 4.7-11.8 mg/l) in children 1-5 years of age. AUC values were 17.4 mg*hr/l (range 11.8-32 mg*hr/L) and 16.5 mg*hr/l (range 11-23.8 mg*hr/l) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on a population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4-5 hours and the bioavailability of the oral suspension is between 50-80%.

5.3 Preclinical safety data
Non-clinical data reveal no specific hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential or toxicity to reproduction. Like some other quinolones, ciprofloxacin has been found to be phototoxic in animals at clinically relevant exposure levels.
Photomutagenicity/photocarcinogenicity data have shown a weak photomutagenic or phototumorogenic effect for ciprofloxacin in in vitro experiments and animal experiments. This effect was found to be similar to that of other gyrase inhibitors.
Articular tolerance studies
Like other gyrase inhibitors, it causes damage to the weight-bearing joints of immature animals.

The degree of cartilage damage varies with age, type, and dose. Damage can be reduced by not overloading the joints. Studies with advanced animals (rat, dog) found no evidence of cartilage damage. With the use of therapeutic doses of ciprofloxacin in young beagle dogs, serious joint changes were detected after 2 weeks, and these changes continued to be observed after 5 months.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients:

Uncoated tablet:

Corn starch
Microcrystalline cellulose
sodium starch glycolate
precipitate silica
magnesium stearate
Talc

Film coating components:

Eudragit EPO
Sodium lauryl sulfate
Stearic acid
Titanium dioxide
magnesium stearate

6.2 Incompatibilities

Not specified.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 The nature and content of the packaging

Containing 14 tablets, Opaque, PVC / PVDC hard Aluminum foil, blister.

6.6 Disposal of residues from the medicinal product for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. LICENSE OWNER

Drogsan İlaçları San. ve Tic. A.Ş.
Oğuzlar Mah. 1370. sok. 7/3
Balgat-ANKARA
Tel: 0 312 287 74 10
Fax: 0 312 287 61 15

8. LICENSE NUMBER

158/48 (in Turkey)

9. FIRST LICENSE DATE/ LICENSE RENEWAL DATE

First license date: 02.12.1991 (in Turkey)
License renewal date: 02.12.2007 (in Turkey)

10. RENEWAL DATE OF SPC

08.05.2020