SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CIPRO-FAR 500, Ciprofloxacin 500 mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Ciprofloxacin (as hydrochloride)

Excipients with known effect:
CIPRO-FAR 500 contains 48 mg Lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong, biconvex film coated tablets, scored on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPRO-FAR 500 film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to the available information on resistance to ciprofloxacin before initiating treatment.

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

Adults

- Lower respiratory tract infections caused by Gram-negative bacteria:
  . exacerbation of chronic obstructive pulmonary disease;
  . broncho-pulmonary infections in cystic fibrosis or bronchiectasis;
  . pneumonia.

- Chronic suppurative otitis media.

- Acute exacerbation of chronic sinusitis especially if caused by Gram-negative bacteria;

- Urinary tract infections.

- Gonococcal urethritis and cervicitis.

- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*.

- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*.

When it is suspected or known that the aforementioned genital tract infections are due to *Neisseria gonorrhoeae*, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility, based on laboratory tests.

- Gastrointestinal tract infections (e.g. traveller's diarrhoea).

- Intra-abdominal infections.

- Infections of the skin and soft tissue caused by Gram-negative bacteria.

- Malignant external otitis.

- Bone and joint infections.

- Treatment of infections in neutropenic patients.

- Prophylaxis of infections in neutropenic patients.

- Prophylaxis of invasive infections caused by Neisseria meningidis.

- Inhalation anthrax (post-exposure prophylaxis and curative treatment).

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa.

- Complicated urinary tract infections and pyelonephritis.

- Inhalation anthrax (post-exposure prophylaxis and curative treatment).

Ciprofloxacin may also be used to treat severe infections in children and adolescents when considered necessary.

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

4.2 Doses and method of administration

The dosage is determined according to the indication, the site of infection and severity, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents, the body weight.

The duration of treatment depends on the severity of the illness and the corresponding clinical and bacteriological course.

Treatment of infections caused by certain bacteria (e.g. Pseudomonas aeruginosa, Acinetobacter or Staphylococci) may require higher doses of ciprofloxacin and co-administration with other appropriate antibacterial agents.

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

Adults

Indications		Daily dose in mg	Total duration of treatment (including potential initial parenteral treatment with ciprofloxacin)
Lower respiratory tract infections		500 mg twice daily to 750 mg twice daily	7 to 14 days
Upper respiratory tract infections	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	At least 10 days, it may be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) up to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal urethritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	At least 14 days
Gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens, including Shigella spp. other than Shigella dysenteriae type 1, and empirical treatment of severe traveller's diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by Shigella dysenteriae type 1	500 mg twice daily	5 days
	Diarrhoea caused by Vibrio cholerae	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days

Skin and soft tissue infections	500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections	500 mg twice daily to 750 mg twice daily	Maximum of 3 months
Treatment or prophylaxis of infections in neutropenic patients. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s), according to official guidelines.	500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to Neisseria meningidis	500 mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for people able to receive treatment by oral route, when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from confirmation of Bacillus anthracis exposure.

Children and adolescents

Indications	**Daily dose in mg**	**Total duration of treatment (including potential initial 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 body weight, twice daily, to 20 mg/kg body weight, twice daily, with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for people able to receive treatment by oral route, when clinically appropriate. Drug administration should be begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight, twice daily, to 15 mg/kg body weight, twice daily, with a maximum of 500 mg per dose	60 days from confirmation of Bacillus anthracis exposure.
Other severe infections	20 mg/kg body weight, twice daily, with a maximum of 750 mg per dose.	According to the type of infections

Elderly patients

Doses administered to elderly patients should be determined according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

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

Creatinine clearance rate [ml/min/1.73 m²]	**Serum creatinine [µmol/l]**	**Oral dose [mg]**
> 60	< 124	See Usual Dose

30 - 60	124 to 168	250 - 500 mg every 12 h
< 30	> 169	250 - 500 mg every 24 h
Patients on haemodialysis	> 169	250 - 500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250 - 500 mg every 24 h

No dose adjustment is required in patients with impaired hepatic function.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets to be swallowed unchewed with liquid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is more rapidly absorbed. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens:
Ciprofloxacin monotherapy is not appropriate for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In these cases, ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal infections (including Streptococcus pneumoniae):
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections:
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae. Unless ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded, ciprofloxacin should be co-administered with another appropriate antibacterial agent. The treatment should be reconsidered if clinical improvement is not achieved after 3 days.

Intra-abdominal infections:
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Traveller's diarrhoea:
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints:
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the microbiological results.

Inhalation anthrax:
Use in humans is based on *in vitro* susceptibility data and on animal experimental data, together with limited data on humans. Physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Vision disorders:
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Children and adolescents:
Official guidelines should be followed when treating children and adolescents with ciprofloxacin. Treatment with ciprofloxacin should only be initiated by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in the weight-bearing joints of immature animals. Safety data from a randomised, double-blind study on the use of ciprofloxacin in children (ciprofloxacin: n = 335; mean age = 6.3 years; comparators: n = 349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) of 7.2% and 4.6%, on Day +42. The incidence of drug-related arthropathy after 1-year of follow-up was 9.0% and 5.7%, respectively. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should only be initiated after a careful risk-benefit assessment, due to possible adverse effects related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis:
Clinical trials have included children and adolescents aged 5 to 17 years old. Experience in children aged 1 to 5 years old is more limited.

Complicated urinary tract infections and pyelonephritis:
Treatment of urinary tract infections with ciprofloxacin should be considered when other treatments cannot be used, and should be based on the microbiological results.
Clinical trials have included children and adolescents aged 1 to 17 years old.

Other specific severe infections:
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections

Hypersensitivity:
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System:
In general, ciprofloxacin should not be given to patients with history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare situations, after microbiological documentation on the causative organism and risk-benefit assessment, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological results justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Tendon inflammation and rupture may occur up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in

elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).

Ciprofloxacin treatment should be discontinued at any sign of tendinitis (e.g. painful swelling, inflammation). Care should be taken to keep the affected limb at rest.

Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity:
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid excessive exposure to direct sunlight or UV radiation during treatment (see section 4.8).

Central Nervous System:

Quinolones are known to trigger seizures or lower the seizure threshold. Cases of epileptic seizures have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders who may be predisposed to seizures. Ciprofloxacin should be discontinued if seizures occur (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis may progress to suicidal ideations, progressing to attempted or completed suicide. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients taking ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness, in order to prevent the development of irreversible conditions (see section 4.8).

Prolongation of the QT interval:
Fluoroquinolones, including CIPRO-FAR 500, should be used with caution in patients with known risk factors of prolongation of the QT interval, such as:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (ex. class I and III anti-arrhythmics, tricyclic antidepressants, macrolides or antipsychotics)
- uncorrected electrolyte alterations (e.g. hypokaliaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including CIPRO-FAR 500, in these populations.
(see sections 4.2 Elderly patients, 4.5, 4.8 and 4.9).

Gastrointestinal System:
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment), may indicate an antibiotic-associated colitis (including life-threatening and possibly fatal outcome) requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should be immediately discontinued and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and Urinary System:
Crystalluria related to ciprofloxacin use has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Renal Impairment:
Since ciprofloxacin is largely excreted unchanged via renal pathway, its dose should be adjusted in patients with impaired renal function, as described in section 4.2, to avoid an increase in adverse drug reactions due to the accumulation of ciprofloxacin.

Hepatobiliary System:
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs or symptoms of hepatic disease (such as anorexia, jaundice, dark urine,

pruritus or abdominal pain), the treatment should be discontinued.

Glucose-6-phosphate Dehydrogenase Deficiency:
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, the potential occurrence of haemolysis should be monitored.

Resistance:
During or following a course of treatment with ciprofloxacin, it is possible to isolate bacteria that demonstrate resistance to this agent, with or without clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudomonas species.

Cytochrome P450:
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentrations of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and the determination of serum concentrations (e.g. theophylline) may be necessary (see section 4.5).

Methotrexate:
Concomitant administration of ciprofloxacin and methotrexate is not recommended (see section 4.5).

Interaction with tests:
The *in vitro* activity of ciprofloxacin against Mycobacterium tuberculosis may give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Lactose:
CIPRO-FAR 500 tablets contain lactose. Patients with rare hereditary disorders of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Medicinal products which prolong the QT interval:
CIPRO-FAR 500, and likewise other fluoroquinolones, should be used with caution in patients concomitantly using other medicinal products known to prolong the QT interval (e.g. class I and III antiarrhythmic drugs, tricyclic antidepressants, macrolides or antipsychotics) (see section 4.4).

Chelation complex formation
The simultaneous administration of ciprofloxacin (oral) and drugs containing multivalent cations and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium or calcium, reduce the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered 1-2 hours before or at least 4 hours after these preparations.
This restriction does not apply to antacids belonging to the H2-receptor blocker class.

Food and dairy products
Dietary calcium, when ingested as part of a regular meal, does not significantly affect ciprofloxacin absorption. However, the simultaneous administration of ciprofloxacin with dairy products or drinks fortified with minerals (e.g. milk, yoghurt, calcium-fortified orange juice) should be avoided, since ciprofloxacin

absorption may be reduced.

Probenecid
Probenecid interferes with the renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases serum ciprofloxacin concentrations.

Metoclopramide
Metoclopramide accelerates the absorption of ciprofloxacin, resulting in a reduction of the time required to reach the maximum plasma concentration. No effect has been noted on the bioavailability of ciprofloxacin.

Omeprazole
The concomitant administration of ciprofloxacin and medicinal products containing omeprazole leads to a slight decrease of the Cmax and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:

Tizanidine
Tizanidine should not be administered concomitantly with ciprofloxacin (see section 4.3). In a clinical study in healthy subjects, there was an increase in serum tizanidine concentrations (Cmax increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when this substance was administered concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated to enhanced hypotensive and sedative effects.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by the concomitant administration of ciprofloxacin, potentially leading to increased plasma methotrexate levels and increased risk of toxic reactions associated with methotrexate. Its concomitant use is not recommended (see section 4.4).

Theophylline
Concomitant administration of ciprofloxacin and theophylline may cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects, which may rarely be life-threatening or even fatal. Serum theophylline concentrations should be monitored during concomitant administration and the theophylline dose reduced, as required (see section 4.4).

Other xanthine derivatives
During concomitant administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), increased serum concentrations of these xanthine derivatives have been reported.

Phenytoin
Simultaneous administration of ciprofloxacin and phenytoin may result in increased or decreased serum phenytoin levels, therefore, monitoring of medicine levels is recommended.

Cyclosporin
A transient increase in creatinine has been observed when ciprofloxacin and cyclosporin are administered concomitantly. Therefore, the serum creatinine levels should be monitored frequently (twice a week) in these patients.

Vitamin K antagonists
Simultaneous administration of ciprofloxacin and vitamin K antagonists may increase anticoagulant effects. The associated risk may vary according to the underlying infection, age and general condition of patients, so the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently, during and immediately after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

Glibenclamide
In particular cases, the concomitant administration of ciprofloxacin and glibenclamide may enhance the action of glibenclamide (hypoglycaemia).

Duloxetine
Clinical studies have shown that the concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme, such as fluvoxamine, may result in an increase of the AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, effects similar can be expected upon concomitant administration (see section 4.4).

Ropinirole
A clinical study demonstrated that concomitant administration of ropinirole and ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isoenzyme, increased the Cmax and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and suitable dose adjustment are recommended, during and immediately after co-administration of this substance with ciprofloxacin (see section 4.4).

Lidocaine
It has been shown in healthy individuals that the concomitant administration of lidocaine and ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isoenzyme, reduces intravenous elimination of lidocaine by 22%. Although treatment with lidocaine has been well tolerated, there may be a possible interaction with side effects after co-administration with ciprofloxacin.

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

Sildenafil
The Cmax and AUC of sildenafil increased approximately two-fold in healthy individuals after an oral dose of 50 mg, administered concomitantly with 500 mg of ciprofloxacin. The risks and benefits should be considered when prescribing the co-administration of ciprofloxacin and sildenafil.

4.6 Pregnancy and lactation

Pregnancy
The available data on ciprofloxacin administration to pregnant women does not indicate malformations or foetal/neonatal toxicity. Animal studies have not shown any direct or indirect harmful effects on reproduction. Effects on immature cartilage have been observed in juvenile and prenatal animals, therefore, the possibility of damage to articular cartilage in the immature human organism/foetus cannot be excluded (see section 5.3).
As a precautionary measure, ciprofloxacin should be avoided during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Hence, the ability to drive and use machines may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADR) are nausea and diarrhoea.

The ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous, and sequential therapy) are listed below, by frequency category. Oral and intravenous ciprofloxacin administration data were taken into account in the frequency analysis.

System Organ Class	**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**	**Unknown frequency (cannot be estimated from the available data)**
Infections and Infestations		Mycotic superinfections	Antibiotic-associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leucopoenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema/ angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolic and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity/ agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially progressing to suicidal tendencies, attempted or actual suicide) (see section 4.4). Hallucinations	Psychotic reactions (potentially progressing to suicidal tendencies, attempted or actual suicide) (see section 4.4).	

System Organ Class	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	Unknown frequency (cannot be estimated from the available data)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including epileptic seizures) (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbances Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disorders (e.g. diplopia)	Colour distortion	
Ear and Labyrinth Disorders			Tinnitus Hearing loss/ Hearing impairment		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, and torsades de points (reported predominantly in patients with risk factors of QT interval prolongation), prolonged QT interval in ECG (see sections 4.4 and 4.9).
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pain Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increased transaminases Increased bilirubin	Hepatic impairment Cholestatic jaundice Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	

System Organ Class	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	Unknown frequency (cannot be estimated from the available data)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus 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 generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. pain in extremities, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramps	Muscular weakness Tendinitis Tendon rupture (predominantly of the Achilles tendon) (see section 4.4) Exacerbation of myasthenia gravis symptoms (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Hematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperidrosis)		
Investigations		Increased blood alkaline phosphatase	Increased amylase		Increased international normalised ratio (INR) (in patients treated with vitamin K antagonists)

Paediatric patients
The aforementioned incidence of arthropathy refers to data collected in studies with adult patients. Arthropathy is commonly reported in children (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure. Overdose symptoms include dizziness, tremor, headache, fatigue, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment, crystalluria and haematuria. Reversible renal toxicity has also been reported.

In addition to routine emergency measures (gastric lavage and administration of activated carbon), monitoring of renal function is recommended, including urinary pH and acidity, if required, in order to prevent crystalluria. Antacids containing calcium or magnesium may theoretically reduce the absorption of ciprofloxacin in the case of overdose.
Only a small percentage of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

In the case of overdose, symptomatic treatment should be instituted. ECG monitoring should be carried out sue to the possibility of prolongation of the QT interval.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anti-infective agents. Antibacterials. Quinolones.

ATC code: J01MA02

Mechanism of action:

As an antibacterial agent belonging to the fluoroquinolone class, the bactericidal action of ciprofloxacin results from inhibition of both type II topoisomerase (DNA gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetic/Pharmacodynamic relationship:
Efficacy depends primarily on the relation between the peak serum concentration (Cmax) and the minimum inhibitory concentration (MIC) of ciprofloxacin, for a given pathogen, and the relation between the area under the curve (AUC) and MIC.

Mechanism of resistance:
In vitro resistance to ciprofloxacin can be acquired through a stepwise process involving target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to most or all active substances within the class.

Mechanisms of resistance such as impermeability and/or active substance efflux pumps may have a variable effect on susceptibility to fluoroquinolones, which depends on the physical-chemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics, such as permeability barriers (common in Pseudomonas aeruginosa) and efflux mechanisms, may affect susceptibility to ciprofloxacin.
Plasmid-mediated resistance encoded by qnr-genes has been reported.

Antibacterial activity spectrum:
Critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains:

EUCAST recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteria	S ≤ 0.5 mg/l	R > 1 mg/l
Pseudomonas	S ≤ 0.5 mg/l	R > 1 mg/l
Acinetobacter	S ≤ 1 mg/l	R > 1 mg/l
*Staphylococcus spp.*1	S ≤ 1 mg/l	R > 1 mg/l
Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/l	R > 0.5 mg/l
Neisseria gonorrhoeae	S ≤ 0.03 mg/l	R > 0.06 mg/l
Neisseria meningitides	S ≤ 0.03 mg/l	R > 0.06 mg/l
Non-species-related critical concentrations*	S ≤ 0.5 mg/l	R > 1 mg/l

1. *Staphylococcus spp.* – critical concentrations for high-dose therapy with ciprofloxacin.
* Non-species-related critical concentrations have been primarily determined from pharmacokinetic/pharmacodynamic data and are independent from MIC distributions for specific species. These values should only be used for species for which no species-specific critical concentrations have been determined and not in cases where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time, for selected species. Local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought when local prevalence of resistance is such that the usefulness of the agent is questionable, at least regarding some types of infections.

Groups of relevant species, according to ciprofloxacin susceptibility (see section 4.4 for Streptococcus species):

Commonly susceptible species

Aerobic Gram-positive microorganisms
Bacillus anthracis (1)

Aerobic Gram-negative microorganisms
Aeromonas spp.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi
*Haemophilus influenzae**
Legionella spp.
*Moraxella catarrhalis**
Neisseria meningitidis
Pasteurella spp.
*Salmonella spp.**
*Shigella spp.**
Vibrio 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 baumannii+
*Burkholderia cepacia+**
*Campylobacter spp.+**
*Citrobacter freundii**
Enterobacter aerogenes
*Enterobacter cloacae**
*Escherichia coli**
Klebsiella oxytoca
*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**

Anaerobic microorganisms
Peptostreptococcus spp.
Propionibacterium acnes

Inherently resistant microorganisms

Aerobic Gram-positive microorganisms
Actinomyces
Enteroccus faecium
Listeria monocytogenes

Aerobic Gram-negative microorganisms
Stenotrophomonas maltophilia

Anaerobic microorganisms
Except as listed above

Other microorganisms
Mycoplasma genitalium
Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates, in approved clinical indications.
+ Resistance rate ≥ 50% in one or more EU countries
($): Natural intermediate susceptibility in the absence of acquired resistance mechanisms.
(1): Studies conducted in animals experimentally infected through inhalation of Bacillus anthracis spores have revealed that the disease can be prevented by early treatment with an antibiotic, immediately after exposure, provided that the number of spores in the organism is reduced to a level below the infective dose. Recommended use in humans is primarily based on in vitro susceptibility data and experimental data in animals, together with limited data in humans. Treatment of adult patients with an oral dose of 500 mg of

ciprofloxacin, twice daily, for two months, is considered to be effective in preventing anthrax infection in humans. The physician should refer to the national and/or international consensus documents regarding treatment of anthrax.
(2): Methicillin-resistant S. aureus very frequently displays co-resistance to fluoroquinolones. The rate of resistance to methicillin is approximately 20 to 50% for all staphylococcal species, being usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of single doses of 250 mg, 500 mg, and 750 mg tablets, ciprofloxacin is readily and extensively absorbed, primarily through the small intestine, reaching peak serum concentrations 1-2 hours later.

Single doses of 100-750 mg lead to dose-dependent peak serum concentrations (Cmax) between 0.56 and 3.7 mg/l. Serum concentrations increase proportionally with doses up to 1,000 mg.

Absolute bioavailability is approximately 70-80%.

Oral administration of 500 mg of ciprofloxacin every 12 hours has been shown to result in an area under the serum concentration-time curve (AUC) equivalent to that observed following intravenous infusion of 400 mg of ciprofloxacin, during 60 minutes, every 12 hours.

Distribution
Ciprofloxacin binding to plasma proteins is low (20-30%). Ciprofloxacin is predominantly found in plasma in non-ionised form and has a large steady-state volume of distribution of 2-3 l/kg body weight. Ciprofloxacin reaches high concentrations in several tissues, such as the lungs (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid) and the urogenital tract (urine, prostate, endometrium), where total concentrations exceed those found in plasma.

Metabolism
Low concentrations of the following four metabolites have been reported: desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). These metabolites display antimicrobial activity in vitro, but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of CYP450 1A2 isoenzymes.

Elimination
Ciprofloxacin is primarily excreted unchanged via the renal route and, to a smaller extent, in the faeces. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Ciprofloxacin excretion (% of dose)		
	Oral administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is 180-300 ml/kg/h and total body clearance is 480-600 ml/kg/h. Ciprofloxacin undergoes glomerular filtration and tubular secretion. Severely impaired renal function leads to an increased ciprofloxacin half-life, of up to 12 h.

Non-renal ciprofloxacin clearance is primarily due to active transintestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. High ciprofloxacin concentrations are found in the bile.

Paediatric patients

Pharmacokinetic data in paediatric patients are limited.

In a study of children, Cmax and AUC were found not to be age-dependent (over one year of age). No considerable increases in Cmax and AUC were observed following repeated doses (10 mg/kg three times daily).

In 10 children with severe sepsis, Cmax was 6.1 mg/l (range: 4.6-8.3 mg/l) following a 1-hour intravenous infusion of 10 mg/kg in children younger than 1 year, compared to 7.2 mg/l (range: 4.7-11.8 mg/l) in children aged 1 to 5 years. The AUC values were 17.4 mg*h/l (range: 11.8-32.0 mg*h/l) and 16.5 mg*h/l (range: 11.0-23.8 mg*h/l) in these age groups, respectively.

These values are within the range reported for adults at the therapeutic doses. Based on pharmacokinetic analysis of paediatric patient populations with various infections, the predicted mean half-life in children is approximately 4-5 hours, and oral suspension bioavailability ranges from 50 to 80%. 4-5 hours and the bioavailability of the oral suspension varies between 50 and 80%.

5.3 Preclinical safety data

Non-clinical data have not revealed any special hazards for humans, based on conventional single dose toxicity, repeated dose toxicity, carcinogenic potential and reproductive toxicity studies.

As with other quinolones, ciprofloxacin is phototoxic in animals exposed to clinically relevant levels. Photomutagenicity/photocarcinogenicity data have revealed a weak photomutagenic or phototumorigenic effect of ciprofloxacin, both in vitro and in animal experiments. This effect was comparable to that observed for other gyrase inhibitors.

Articular tolerability
As reported for other gyrase inhibitors, ciprofloxacin causes damage to large weight-bearing joints in immature animals. The extent of cartilage damage varies according to age, species and dose. The lesion can be reduced by decreasing the weight borne by the affected joints. Studies in adult animals (rats, dogs) have not revealed any evidence of cartilage lesions. In a study in young beagle dogs, therapeutic doses of ciprofloxacin caused severe articular changes after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core –
Lactose
Sodium starch glycolate
Povidone
Sodium stearyl fumarate.

Coating –
Hypromellose
Polyethylene glycol 400
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30º C.

6.5 Nature and contents of the container

Primary packaging: PVC/Aluminium blisters.

Pack size of 16 film-coated tablets.

6.6 Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

GP – Genéricos Portugueses, Lda.
Rua Henrique Paiva Couceiro, 29, Venda Nova
2700-451 Amadora
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

04401/06690/REN/2018

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