SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

CIPROMED - 500 (Ciprofloxacin Tablets USP 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg ciprofloxacin (as hydrochloride)

Preservatives-Methyl Paraben: 0.800 mg/tab

Propyl Paraben: 0.079 mg/tab

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Off white coloured caplet shaped coated tablet having “CIPRO” on one side and “500” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin 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 available information on resistance to ciprofloxacin before commencing therapy.

Adults

• Lower respiratory tract infections due to Gram-negative bacteria

- pneumonia
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

• Chronic suppurative otitis media

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

• Acute pyelonephritis

• Complicated urinary tract infections

• Bacterial prostatitis

• 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*

• Intra-abdominal infections

• Infections of the skin and soft tissue caused by Gram-negative bacteria
• Infections of the bones and joints
• Inhalation anthrax (post-exposure prophylaxis and curative treatment)
Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to abacterial infection.
In **exacerbations of chronic obstructive pulmonary disease** Ciprofloxacin should be used only when it is consideredinappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
In **uncomplicated acute cystitis** Ciprofloxacin should be used only when it is considered inappropriate to use otherantibacterial agents that are commonly recommended for the treatment of these infections.
Children and adolescents
• Broncho-pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis
• Complicated urinary tract infections and acute pyelonephritis
• Inhalation anthrax (post-exposure prophylaxis and curative treatment)
Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to benecessary.
Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severeinfections in children and adolescents (see sections 4.4 and 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Method of administration:

Yourdoctorwill decide on how many CIPROMED 500 tablets you should take
Dosage will depend on the type of infection you have.
Adults: 500mg two to three times a day.
Children: 250mg two to three times a day.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course
Treatment of infections due to certain bacteria (e.g. Pseudomonas aeruginosa, Acinetobacter or Staphylococci) mayrequire higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents

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

Indications		**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	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 up to 3 months
Urinary tract infections (see section 4.4)	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 can 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) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500mgasasingle dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella*spp. other than *Shigelladysenteriae*type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by *Shigelladysenteriae*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
Infections of the skin and soft tissue		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	max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		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 meningitides*		500mgasasingle dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons 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 the confirmation of *Bacillus anthracis*exposure

Paediatric population

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including 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 persons able to receive treatment by oral route whenclinically appropriate. Drug administration should begin as soonas 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 the 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

Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinineclearance.

Patients with renal and hepatic impairment

Recommended starting 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 Usual Dosage.
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

Kidney or Liver problems:

If you have any kidney or liver problems, you may be given a lower dose.

Urine Tests:

Taking CIPROMED 500 tablets may affect the results of some urine tests. If you are going to have a urine test, it is important to tell your doctor that you are taking these tablets.

If you take more CIPROMED 500 tablets than you should:

If you take more CIPROMED 500 tablets than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen: feeling confused or dizzy, loss of consciousness, fits, feeling sick or blood in your stools.

If you forget to take CIPROMED 500 tablets:

If you forget a dose, take your next dose as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for the one you have missed.

If you stop taking CIPROMED 500 tablets:

Keep these tablets until your doctor tells you to stop. Do not stop taking this medicine just because you feel better. If you do not complete the prescribed course of your medicine, your infection may come back and get worse again.

If you have any other question on the use of this medicine, please contact your doctor or pharmacist.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients.

Concomitant administration of ciprofloxacin and tizanidine.

4.4 Special warnings and special precautions for use

The use of ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past whenusing quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with ciprofloxacinshould only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (seealso section 4.3).

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drugreactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) havebeen reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing riskfactors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reactionand patients should be advised to contact their prescriber for advice.

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriateantibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections

Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae isolates*.

Therefore, ciprofloxacin should be adminstered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae*can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered incombination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin resistant *Neisseriagonorrhoeae*can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should bereconsidered.

Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections –varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in*Escherichia coli* to quinolones.
The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to beassociated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regardsthe increasing resistance level of *Escherichia coli* to quinolones.
Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.
Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens inthe countries visited.
Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of themicrobiological documentation.
Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data.Treating physicians should refer to national and/or international consensus documents regarding the treatment ofanthrax.
Paediatric population
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatmentshould be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections inchildren and adolescents.
Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from arandomised double-blind study on ciprofloxacin use 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-relatedarthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, anincidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-relatedarthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after acareful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue (see section4.8)..
Broncho-pulmonary infections in cystic fibrosis

Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treatingchildren between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, andshould be based on the results of the microbiological documentation.

Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when othertreatments cannot be used, or after failure to conventional therapy and when the microbiological documentation canjustify a ciprofloxacin use.

The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated inclinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with theseinfections.

Hypersensitivity

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

Musculoskeletal System

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolonetreatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism andevaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certainsevere infections, particularly in the event of failure of the standard therapy or bacterial resistance, where themicrobiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early aswithin 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up toseveral months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients,patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids.Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with ciprofloxacin should be discontinuedand alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g.immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated(see section 4.8).

Vision disorders

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

Photosensitivity

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

Central Nervous System

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of statusepilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases,ciprofloxacin should be discontinued.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacinshould be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (seesection 4.8).

Cardiac disorders

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors forprolongation of the QT interval such as, for example:

• congenital long QT syndrome

• concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

• uncorrected electrolyte imbalance (e.g. hypokalaemia, 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 takenwhen using fluoroquinolones, including ciprofloxacin, in these populations. (See section 4.2 Elderly patients, section 4.5,section 4.8, section 4.9).
Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g.,glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoringof blood glucose is recommended (see section 4.8).
Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment)may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment(see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated.Anti-peristaltic drugs are contraindicated in this situation.
Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacinshould be well hydrated and excessive alkalinity of the urine should be avoided.
Impaired renal function
Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impairedrenal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation ofciprofloxacin.
Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). Inthe event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tenderabdomen), 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, potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a 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 concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine,**agomelatine**). 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 determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in-vitro* activity of ciprofloxacin against Mycobacterium tuberculosis might give false negative bacteriological testresults in specimens from patients currently taking ciprofloxacin.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and ofaortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection,sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valveshave been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of othertherapeutic options in patients with positive family history of aneurysm disease, or congenital heart valve disease, or inpatients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or heart valve disease, or in presence ofother risk factors or conditions predisposing

- for aortic aneurysm and dissection and heart valve regurgitation/ incompetence (e.g. connective tissue disorders such asMarfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis).
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

4.5 Interaction with other FPPs and other forms of interaction

Effects of other products on ciprofloxacin:

Drugs known to prolong QT interval

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QTinterval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements(e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate),sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calciumreduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or atleast 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

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

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction ofCmax and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedlyinhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical dataare available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can beexpected upon concomitant administration **(**see 'Cytochrome P450' in section 4.4).

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthysubjects, there was an increase in serum tizanidine concentration (Cmax increase: 7-fold, range: 4 to 21-fold; AUCincrease: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentiallyleading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophyllineconcentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During thecombination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary(see section 4.4).

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrationsof these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoinsuch that monitoring of drug levels is recommended.

Cyclosporin

A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporincontainingmedicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control theserum creatinine concentrations in these patients.

Vitamin K antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The riskmay vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin tothe increase in INR (international normalised ratio) is difficult to assess. The INR should be monitored frequently duringand shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol,phenprocoumon, or fluindione).

Duloxetine

In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data areavailable on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration(see section 4.4).

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP4501A2 isozyme, results in an increase of Cmax and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%.Although lidocaine treatment was well

tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised (seesection 4.4).

Sildenafil

Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg givenconcomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly withsildenafil taking into consideration the risks and the benefits.

Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended

4.6 Pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformativeorfeto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immatureorganism / foetus (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Breast-feeding

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. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

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

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin (oral, intravenous, and sequentialtherapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

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`	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (lifethreatening) Bone marrow depression (life threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (lifethreatening) (see section 4.4) Serum sickness like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of

					antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia Hypoglycaemic coma (see section 4.4)		
Psychiatric Disorders*		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression(potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	Mania, incl. hypomania
Nervous System Disorders*		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye Disorders*			Visual disturbances(e.g. diplopia)	Visual colour distortions	
Ear and Labyrinth Disorders*			Tinnitus, Hearing loss / Hearing impaired		
Cardiac Disorders**			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (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 pains, Dyspepsia Flatulence	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash, Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens- Johnson Syndrome (potentially lifethreatening) Toxic epidermal necrolysis (potentially life- threatening)	Acute generalised exanthematous pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), Arthralgia	Myalgia, Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*		Asthenia Fever	Oedema, Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalized ratio increased (in patients treated with Vitamin K antagonists)

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and ofregurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (seesection 4.4).

Paediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults.In children, arthropathy is reported to occur commonly (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuedmonitoring of the benefit/risk balance of the medicinal product.

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 beenreported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominaldiscomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has beenreported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon it is recommended tomonitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept wellhydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin inoverdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken,because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type IItopoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair andrecombination.

Pharmacokinetic /Pharmacodynamic relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimuminhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve(AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNAgyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinicalresistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substanceswithin 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 permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Enterobacteriaceae	S ≤ 0.5 mg/L	R > 1 mg/ L
Pseudomonas spp.	S ≤ 0.5 mg/L	R > 1 mg/ L
Acinetobacter spp.	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 meningitidis	S ≤0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤0.5 mg/L	R > 1 mg/ L

1 Staphylococcus spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Bacillus anthracis (1)
Aerobic Gram-negative micro-organisms
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 micro-organisms
Mobiluncus
Other micro-organisms
Chlamydia trachomatis ($)
Chlamydia pneumoniae ($)
Mycoplasma hominis ($)

Mycoplasma pneumoniae ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis ($)* *Staphylococcus spp. *(2)*
Aerobic Gram-negative micro-organisms *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 micro-organisms *Peptostreptococcus spp.* *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *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 mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.

(2): Methicillin-resistant S. aureus very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hourslater.

Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (Cmax) between 0.56 and 3.7mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70-80%.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve(AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blisterfluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1),sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro*antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h. Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children Cmax and AUC were not age-dependent (above one year of age). No notable in

In 10 children with severe sepsis Cmax was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. 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 the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokineticanalysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and thebioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeateddose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data onphotomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro*and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immatureanimals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced bytaking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In astudy in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks oftreatment, which were still observed after 5 months.crease in Cmax andAUC upon multiple dosing (10 mg/kg three times daily) was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Microcrystalline Cellulose, Methyl Paraben, Propyl Paraben, Talc, Magnesium Stearate, Sodium Starch glycolate , Colloidal Anhydrous Silica, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol – 6000, Talc, Titanium Dioxide, Sodium Lauryl Sulphate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25^{o}C in a dry place. Protect from light.

6.5 Nature and contents of container

Alu-PVC blister pack of 10x10 tablets packed in carton along with Pack Insert

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Milan Laboratories (India) Pvt. Ltd.
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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

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