**Prescribing Information (Summary of Product Characteristics)**

**1. Name of the medicinal product**

Strength: 500 mg

Brand Name: CIPROBID 500

INN Name: Ciprofloxacin Tablet USP 500 mg

**2. Qualitative and quantitative composition** **Each Film coated tablet contains** Ciprofloxacin Hydrochloride USP

Equivalent to Ciprofloxacin 500 mg

Excipients q.s.

Colour- Titanium Dioxide

For full list of excipients see section 6.1

**3. Pharmaceutical form:**

Form: Tablet

◆ **Description**:

CIPROBID 500 Tablet is white colored, caplet shaped, biconvex film coated tablets, plain on both sides.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indication**

Ciprofloxacin tablets are indicated for the treatment of the following infections.

**Adults**

- Lower respiratory tract infections due to Gram-negative bacteria
- exacerbations of chronic obstructive pulmonary disease
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- pneumonia
- Chronic suppurative otitis media

- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections & Genital tract infections
- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- 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)

**Children and adolescents**

- Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure and curative treatment)

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

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

## 4.2 Posology and Method of Administration:

Posology

The dosage is determined by the indication, the severity and the site of the infection, 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 on the clinical and bacteriological course.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require 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 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 (potentially including initial parenteral treatment** |
|---|---|---|

| | | | |
|---|---|---|---|
| | | | **with ciprofloxacin)** |
| Infections of the lower respiratory tract | | 500mg twice daily to 750 mg twice daily | 7 to 14 days |
| Infections of the upperrespiratory tract | Acute exacerbation of chronic sinusitis | 500 mg twice dailyto 750 mg twice daily | 7 to 14 days |
| | Chronic suppurative otitis media | 500 mg twice dailyto 750 mg twice daily | 7 to 14 days |
| | Malignant external otitis | 750 mg twice daily | 28 days up to 3 months |
| Urinary tract infections | Uncomplicated cystitis | 250mg twice dailyto 500 mg twice daily | 3 days |
| | | In pre-menopausal women, 500 mgsingle dose may be used | |
| | Complicated cystitis, Uncomplicated pyelonephritis | 500 mg twice daily | 7 days |
| | Complicated pyelonephritis | 500 mg twice dailyto 750 mg twice daily | at least 10 days, it can be continued for longer than 21days in some specific circumstances (such as abscesses) |
| | Prostatitis | 500 mg twice dailyto 750 mg | 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |

| | | | |
|---|---|---|---|
| | | twice daily | |
| Genital tract infections | Gonococcal uretritis and cervicitis | 500 mg as a single dose | 1 day (single dose) |
| | Epididymo-orchitis and pelvic inflammatory diseases | 500 mg twice dailyto 750 mg twice daily | at least 14 days |
| Infections of the gastro- intestinal tract and intraabdominal infections | Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae*type 1 and empirical treatment of severetravellers' 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 | 7 days |
| | | twice daily | |
| | Intra-abdominal infections due toGram-negative bacteria | 500 mg twice dailyto 750 mg twice daily | 5 to 14 days |
| Infections of the skin and soft tissue | | 500mg twice dailyto 750 mg twice daily | 7 to 14 days |
| Bone and joint infections | | 500 twice daily to750mg twice daily | max. of 3 months |

| | | |
|---|---|---|
| Treatment of infections or prophylaxis of infections in neutropenic patients 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 meningitidis* | 500 mg as a single 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 when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed | 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 |

| | | |
|---|---|---|
| exposure | | |
| Other severe infections | 20 mg/kg body weight twice daily with a maximum of 750 mg perdose | According to the type ofinfections |

Elderly Patients

Elderly patients should receive a dose selected according to the severity of the infection and thepatient's creatinine clearance.

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 |

In patients with impaired liver function no dose adjustment is required.

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

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

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it isrecommended 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
- Concomitant administration of ciprofloxacin and tizanidine

## 4.4 Special warnings and precautions for use

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake offluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

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 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

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may becaused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates.

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

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

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 fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* toquinolones.

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 in the countries visited.

Infections of the bones and joints

Ciprofloxacin should be used in combination with other antimicrobial agents depending on theresults of the microbiological 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 of anthrax.

Paediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance.

Ciprofloxacin treatment should be initiated only 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 weight-bearing joints of immature animals. Safety data from a randomised 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-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug- related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

*Broncho-pulmonary infections in cystic fibrosis*

Clinical trials have included children and adolescents aged 5-17 years. More limited experience isavailable in treating children 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, and should 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 other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify 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 and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, 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 data mayjustify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.

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

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be aggravated.

Vision disorders

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

Central Nervous System

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus 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/thought culminating in attempted suicide or

completed suicide. In the occurrence of such 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 receiving 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 an irreversible condition.

Cardiac disorders

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation 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 anti- arrhythmics, 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 taken when using fluoroquinolones, including ciprofloxacin, in these populations.

Hypoglycaemia

As with other quinolones, hypoglycaemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended.

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. 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. Patients receiving ciprofloxacin should 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 impaired renal function as described in to

avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), 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.

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended.

Interaction with tests

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

## 4.5 Interaction with other medicinal products 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 QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

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), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin.
Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 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 increases ciprofloxacin 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 of Cmax and AUC of ciprofloxacin

Effects of ciprofloxacin on other medicinal

products: Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (Cmax increase: 7-fold, range: 4 to 21-fold; AUC increase: 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, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended .

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal.

During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives

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

Phenytoin

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

Ciclosporin

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

Vitamin K antagonists

Simultaneous administration of ciprofloxacin with a vitamin k antagonist may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and 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 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 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.

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.

Sevelamer

The bioavailability of ciprofloxacin is reduced by the concomitant administration with sevelamer(up to 50%), therefore, it is recommended that the two should not be taken concomitantly.

Sildenafil

Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after an oraldose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be usedprescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration.

Zolpidem

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or foeto/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 immature organism / foetus.

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,

ciprofloxacinshould 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 orto operate machinery may be impaired.

### 4.8 Undesirable effects

a) Summary of the safety profile

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

b) Tabulated list of adverse reactions

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. Thefrequency 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 availabledata)** |
|---|---|---|---|---|---|
| Infections and Infestations | | Mycotic superinfections | | | |
| Blood and Lymphatic System Disorders | | Eosinophilia | Leukopenia<br>Anaemia<br>Neutropenia<br>Leukocytosis<br>Thrombocytopenia<br>Thrombocytaemia | Haemolytic anaemia<br>Agranulocytosis<br>Pancytopenia (life-threatening)<br>Bone marrow depression (life-threatening) | |
| Immune System Disorders | | | Allergic reaction<br>Allergic oedema / angioedema | Anaphylactic reaction<br>Anaphylactic shock (life-threatening)<br>Serum sickness-like | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | reaction | |
| Metabolism and Nutrition Disorders | | Decreased appetite | Hyperglycaemia<br>Hypoglycaemia | | |
| Psychiatric Disorders | | Psychomotor hyperactivity /agitation | Confusion and disorientation<br>Anxiety reaction<br>Abnormal dreams<br>Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide)<br>Hallucinations | Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) | Mania<br>Hypomania |
| Nervous System Disorders | | Headache<br>Dizziness<br>Sleep disorders<br>Taste disorders | Par- and Dysaesthesia<br>Hypoaesthesia<br>Tremor<br>Seizures (including status epilepticus<br>Vertigo | Migraine<br>Disturbed coordination<br>Gait disturbance<br>Olfactory nerve disorders<br>Intracranial hypertension and pseudotumour cerebri | Peripheral neuropathy and polyneuropathy |
| Eye Disorders | | | Visual disturbances | Visual colour distortions | |
| Ear and Labyrinth Disorders | | | Tinnitus<br>Hearing loss / Hearing impaired | | |

| | | | | | |
|---|---|---|---|---|---|
| Cardiac Disorders | | | Tachycardia | | Ventricular arrhythmia and torsades de pointes (reported predominantly inpatients with riskfactors for QT prolongation), ECG QT prolonged |
| Vascular Disorders | | | Vasodilatation Hypotension Syncope | Vasculitis | |
| Respiratory, Thoracic and Mediastinal Disorders | | | Dyspnoea (including asthmatic condition) | | |
| GastrointestinalDisorders | Nausea Diarrhoea | Vomiting Gastrointestinaland abdominal pains Dyspepsia Flatulence | Antibiotic associated diarrhoea including pseudomembranouscolitis | Pancreatitis | |
| HepatobiliaryDisorders | | Increase in transaminasesIncreased bilirubin | Hepatic impairment Cholestatic icterus Hepatitis | Liver necrosis (very rarely progressing to life-threatening hepatic failure) | |
| Skin and Subcutaneous Tissue Disorders | | Rash Pruritus Urticaria | Photosensitivity reactions | Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic | Acute generalised exanthematouspustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms |

| | | | | | |
|---|---|---|---|---|---|
| | | | | epidermal necrolysis (potentially life-threatening) | (DRESS) |
| Musculoskeletal, Connective Tissue and Bone Disorders | | Musculoskeletal pain (e.g. extremity pain, back pain, chest pain)<br>Arthralgia | Myalgia<br>Arthritis<br>Increased muscle tone and cramping | Muscular weakness<br>Tendinitis<br>Tendon rupture (predominantly Achilles tendon)<br>Exacerbation of symptoms of myasthenia gravis | |
| Renal and Urinary Disorders | | Renal impairment | Renal failure<br>Haematuria<br>Crystalluria<br>Tubulointerstitial nephritis | | |
| General Disorders and Administration Site Conditions | | Asthenia<br>Fever | Oedema<br>Sweating (hyperhidrosis) | | |
| Investigations | | Increase in blood alkaline phosphatase | Prothrombin level abnormal<br>Increased amylase | | International normalised ratio increased (in patients treated |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | with Vitamin K antagonists) |

Paediatric population

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly

### 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.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria.

Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. 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** Therapeutic

classification: J01MA02 Activity:

Ciprofloxacin is a synthetic 4-quinolone derivative antibacterial agent of the

fluoroquinolone class. Mechanism of action:

As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Spectrum of activity:

**Breakpoints:**

BSAC: S[ 1ml/L; Rμ 2mg/l, except Pseudomonas R μ 8mg/ml and UTI R μ

8mg/L. NCCLS: S [ 1mg/1; I = 2mg/l; R μ 4mg/l.

**Susceptibility**

The prevalence of the acquired resistances can vary for some species geographically and with time. Therefore, it is important to obtain information on local resistance patterns, particularly when treating more severe infections.

| **Organism** | **Prevalence of Resistance** |
|---|---|
| **Sensitive:** | |
| **Gram-positive bacteria** | |
| Staphylococcus aureus (methicillin sensitive) | 0-14% |
| Streptococcus agalactiae | 0-17% |
| **Gram-negative bacteria** | |
| Acinetobacter baumanii | 6-93% |
| Acinetobacter spp. | 14-70% |
| Aeromonas hydrophila | |
| Campylobacter jejuni/coli | 0-82% |
| Citrobacter freundii | 0-4% |
| Enterobacter aerogenes | |
| Enterobacter cloacae | 0-3% |
| Enterobacter spp | 3-13% |
| Escherichia coli | 2-7% |
| Haemophilus influenzae | 0-1% |
| Klebsiella spp. | 2-21% |
| Moraxella catarrhalis | |
| Morganella morganii | 1-2% |
| Neisseria gonorrhoeae | 5% |
| Plesiomonas shigelloides | |
| Proteus mirabilis | 0-10% |
| Proteus vulgaris | 4% |
| Providencia spp. | 4% |
| Pseudomonas aeruginosa | 1-28% |
| Salmonella spp. | |
| Salmonella typhi | 0-2% |
| Serratia liquefaciens | |
| Serratia marcescens | 23% |
| Shigella spp | |
| Vibrio spp | |
| Yersinia enterocolitica | |
| **Anaerobes*** | |
| Peptococcus spp. | - |
| Peptostreptococcus spp. | - |
| Veillonella parvula | - |

| | |
|---|---|
| **Other pathogens** | |
| Legionella pneumophila | - |
| Intermediate | |
| Viridans streptoeocci | 5-9% |
| Streptococcus pneumonziae | 2.8% |
| Streptococcus pyogenes | 2.8% |
| **Other pathogens** | |
| Chlamydia spp | - |
| **Resistant** | |
| **Gram-positive aerobes** | |
| Enterococcus spp | - |
| Staphylococcus aureus (methicillin resistant) | 48-90% |
| **Gram-negative aerobes** | |
| Stenotrophomonas maltophila | - |
| Flavobacterium menmgosepticum | - |
| Nocardia asteroides | - |
| **Anaerobes** | |
| Bacteroides_fragilis | - |
| Bacteroides thetaiotaomicron | - |
| Clostridium difficile | - |

The information provided below gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

* Ciprofloxacin is not considered the drug of first choice for treatment of infections with anaerobes.

In-vitro investigations have shown that resistance to ciprofloxacin is commonly due to mutations in bacterial topoisomerases and usually develops slowly and gradually ("multiple-step" type).

Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the class.
Impermeability and/or drug efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various drugs within the class and the affinity of transport systems for each drug.

## 5.2 Pharmacokinetic properties

### Absorption

After oral administration, ciprofloxacin is predominantly absorbed from the duodenum and upper jejunum, and reaches peak serum concentrations within 60-90 min. After single doses of 250mgand 500mg Cmax values are about 0.8-2.0mg/1 and 1.5-2.9mg/1 respectively

The absolute bioavailability is approximately 70 to 80%. Cmax- and AUC-values are proportionally increased with the dose.

Food intake has no effect on the plasma concentration profile of

ciprofloxacin.

**Distribution**

The steady-state volume of distribution of ciprofloxacin is 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma innon-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravasal space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.

**Metabolism / Elimination**

Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance liesbetween 3 and 5ml/min/kg, and total clearance amounts to 8-10ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.

Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3show antibacterial activity comparable with or smaller than nalidixic acid. M 4 with the lowest quantity, has an antimicrobial activity very much corresponding to norfloxacin.

Excretion after oral administration (in % of the ciproftoxacin dose):

| | urine | faeces |
|---|---|---|
| Ciprofloxacin | 44.7 | 25.0 |
| Metabolites | 11.3 | 7.5 |

The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral and after intravenousadministration.

Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renalfunction must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

**5.3 Preclinical safety data**

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the

growth phase ofjuvenile animals. Other preclinical effects were observed only at exposures, sufficiently in excessof the maximum human exposure, that make concern for human safety negligible in respect of animal data.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients :

**Tablet core**

Corn Starch,

Sodium starch

Glycolate,

Magnesium

Stearate, Purified

water, Talc,

Croscarmellose

Sodium, Colloidal

Silicon Dixoide,

Film-coating
Sheffcoat PVA -White(5Y00122) In-House
Polyvinyl Alcohol Polyethylene Glycol Titanium Dioxide Talc

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life :

36 months

### 6.4 Special precautions for storage :

Store below $30^0$ C. Protect from light.

### 6.5 Nature and contents of container :

10 x 10 tablets in blister packs (ALU-PVC)

### 6.6 Special precautions for disposal and other handling

"Any unused product or waste material should be disposed of in accordance with local requirements";

**7. Marketing Authorization holder and Manufacturing site Address**

Pinnacle Life Science Pvt. Ltd.,
Mahendra Industrial Estate, Ground Floor, Plot No.
109-D,Road No. 29, Sion (East), Mumbai, India

**Manufacturing site Address**

Pinnacle Life Science Pvt. Ltd.,
Khasra No. 1328-1330, Village -Manpura, Tehsil -
Baddi,Dist . Solan, Himachal Pradesh (INDIA)

**8. Marketing Authorization number**
TAN 21 HM 0380

**9. Date of renewal of the Authorization**
Not Applicable

**10. Date of revision of the text**
April, 2022