SMPC OF CIPROFLOXACIN TABLETS USP 500 MG

1. Name of drug product

CIPROFLOXACIN TABLETS USP 500 MG

1.1 (Trade) name of product

CIPROFLOXACIN TABLETS USP 500 MG

1.2 Strength

Ciprofloxacin 500 mg

1.3 Pharmaceutical Dosage Form

Tablets

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each film coated tablet contains:

Ciprofloxacin Hydrochoride USP

Equivalent to ciprofloxacin……..500 mg

Excipient ……..q.s.

Colour: Approved colour used

For a list of excipients, see section 6.1

3. PHARMACEUTICAL DOSAGE FORM

A white coloured oval shaped biconvex film coated tablet having embossed “MAXHEAL” on one side and “CIPRO 500” on other side each tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ciprofloxacin film-coated tablets are indicated for the treatment of the following infections. Special

attention should be paid to available information on resistance to Ciprofloxacin before commencing therapy.

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

Adults

• Lower respiratory tract infections due to Gram-negative bacteria

- acute 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

• Uncomplicated acute cystitis

In uncomplicated acute cystitis Ciprofloxacin film-coated tablets should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis

• Complicated urinary tract infections

• Bacterial prostatitis

• Genital tract infections

- gonococcal uretritis and cervicitis due to susceptible Neisseria gonorrhoeae

- epididymo-orchitis including cases due to Neisseria gonorrhoeae

- pelvic inflammatory disease including infections due to Neisseria gonorrhoeae

• 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)

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

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 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		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
Urinary tract infections	Uncomplicated cystitis	50 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Acute uncomplicated pyelonephritis	500 mg twice daily	7 days
	Acute 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)
	Bacterial prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections Genital tract infections	Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	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
	Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	500 mg as a single dose	1 day (single dose)
Infections of the 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 travellers' 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	500 mg twice daily to	5 to 14 days

	Gram-negative bacteria	750 mg twice daily	
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.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
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)**
Broncho pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and acute 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 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

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance**.**

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

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

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. 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 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 excBPients

• 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 when using quinolone or fluoroquinolone containing products. Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious

adverse drug reactions affecting different, sometimes multBPle, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any adverse reaction and 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 coadministered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumonia)

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 disease may be caused by fluoroquinolones-resistant Neisseria gonorrhoeae isolates.

Therefore, Ciprofloxacin should be administered 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 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 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 m 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 results 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 is available 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 in 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 guidelines, 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 and may be life-threatening. If such reaction occurs, Ciprofloxacin should be discontinued and an adequate medical treatment required.

Tendinitis and tendon ruptureCiprofloxacin 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 microbiological data may justify the use of Ciprofloxacin.

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several 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 discontinued and 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.

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 discontin. 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 Ciprofloxacin should 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.

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.

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 of aortic 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 valves have been reported in patients receiving fluoroquinolones.
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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing
• for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
• 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.

Dysglycaemia
As with other 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 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 Pseudominas species.

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of Ciprofloxacin and tizanidine is contraindicated. 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.

Vision disorders

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on Ciprofloxacin

<u>Drugs known to prolong QT interval</u>

Ciprofloxacin like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA or III antiarrhythmics, 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 or lanthanum carbonate), 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 the preparation.

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. Coadministration 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:

<u>Tizanidine</u>

Tizanidine must not be administered together with Ciprofloxacin. 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 (oxpentBPhylline), 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.

Cyclosporin

A transient rise in the concentration of serum creatinine was observed when Ciprofloxacin and cyclosporin 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 anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of Ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after coadministration 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 coadministration 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 co-administration with Ciprofloxacin are advised.

Sildenafil

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

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, 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 ('Cytochrome P450' in section 'Special warnings and precautions for use).

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 feto/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, 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 reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin (oral, intravenous and sequential therapy) 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		Eosinophilia	Leukopenia	Haemolytic	

Lymphatic System Disorders			Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	anaemia Agranulocytosis Pancytopenia (life threatening) Bone marrow depression (life threatening)	
Immune System Disorders			Allergic reaction Allergic oedema/ angiooedema	Anaphylactic reaction Anaphylactic shock (life threatening) Serum sickness like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia		Hypoglycaemic coma
Psychiatric disorders*		Psychomotor hyperactivity/ agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideation/thoughts or suicide attempts and completed suicide) Hallucination	Psychotic reactions (potentially culminating in suicidal ideations/thought or suicide attempts and completed suicide)	Mania, hypomania
Nervous System Disorders*		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and psuedotumor	PerBPheral neuropathy and polyneuropathy

				cerebri	
Eye Disorders*			Visual disturbances	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
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 diarrhoea including pseudomembraneous colitis (very rarely with possible fatal outcome)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased 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	Acute generalised exanthematous pustulosis (AGEP), DRESS

				syndrome (potentially life threatening) Toxic epidermal necrolysis (potentially life threatening)	
Musculoskeletal, Connective Tissue and Bone 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) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

*Very rare case of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multBPle, system organ classes and senses (including reactions such as tendonitis, tendon rapture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment in 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.

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones),

and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Paediatric patients

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

Phenoxymethylpenicillin has low toxicity. However, if there is gross renal impairment, the medicine may accumulate in the blood, and the dose should be reduced accordingly. Large quantities of parenterally administered penicillin (greater than 20 million units per day) have been associated with CNS effects e.g. lethargy, confusion, epileptiform seizures.

Treatment

Management of overdose should include monitoring of electrolyte balance, cardiovascular status and renal function.

Penicillin may be removed by haemodialysis. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

An overdose of 12g 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 of overdose may include dizziness, tremor, headaches, 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 e.g. ventricular emptying followed by medical carbon,, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.

Calcium or magnesium containing antacids may theoretically reduce the absorption of Ciprofloxacin in overdoses.

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 Pharmacodynamics properties

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02

Mechanism of Action:

As a fluoroquinolones antibacterial agent, the bactericidal action of Ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimum inhibitory 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 DNA gyrase 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 multBPle mutations generally result in clinical resistance 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 the susceptibility to fluoroquinolones, which depends on physiochemical 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 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:

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 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

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 ($)
Staphylococcus spp. *(2)
Aerobic Gram-negative microorganisms
Acinetobacter baumannii^{+}
Burkholderia cepacia^{+}*
Campylobacter spp.$^{+}$*
*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 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

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 hours later.

Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (Cmax) between 0.56 and 3.7 mg/L. Serum concentration 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 400mg Ciprofloxacin given over 60 minutes every 12 hours.

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 blister fluid), 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 (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylCiprofloxacin (M4). 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction. Like a number of other quinolones, Ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic ophototumorigenic 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 immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, Ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. Pharmaceutical Particulars

6.1 List of excBPients

Microcrystalline cellulose

Lactose

Carmellose sodium

Starch for paste

Talcum

Sodium starch glycolate

Colloidal silicon dioxide

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry place, protect from light.

6.5 Nature and contents of container

10 X 10 Alu-Alu blister

7. Marketing authorization holder

MAXHEAL PHARMACEUTICALS (INDIA) LTD.

J-7, M.I.D.C., Tarapur Industrial Area,

Boisar-401506, Dist .Palghar, India.

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorization

NA

10. Date of revision of the text

NA