1. NAME OF THE MEDICINAL PRODUCT

(Ciprofloxacin 500 Tablets) Ciprofloxacin 500mg BP Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains, Ciprofloxacin Hydrochloride BP Eq. to Ciprofloxacin 500 mg.

Excipients Q.S

{For a full list of excipients, see section 6.1}]

3. PHARMACEUTICAL FORM

White capsule shaped biconvex film coated tablet having break line on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

It is 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
- Exacerbations of chronic obstructive pulmonary disease
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- Pneumonia
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infection
- Genital tract infections - gonococcal uretritis 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
- 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
- Malignant external otitis
- Infections of the bones and joints
- Prophylaxis of invasive infections due to Neisseria meningitidis
- 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 in cystic fibrosis caused by Pseudomonas aeruginosa
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is 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

Infection of the lower respiratory tract – 500 mg twice daily to 750 mg twice daily for 7 to 14 days

Infections of the Upper respiratory (Acute exacerbation of chronic sinusitis) - 500 mg twice daily to 750 mg twice daily for 7 to 14 days

Chronic suppurative otitis media- 500 mg twice daily to 750 mg twice daily for 7 to 14 days

Malignant external otitis: 750 mg twice daily for 28 days up to 3 months.
Urinary tract infection (Uncomplicated cystitis)- 250 mg twice daily to 500 mg twice daily for 3 days. In pre-menopausal women, 500 mg single dose may be used.

Complicated cystitis, Uncomplicated pyelonephritis – 500 mg twice daily for 7 days.
Complicated pyelonephritis – 500 mg twice daily to 750 mg twice daily for at least 10 days, it can be continued for longer than 21 days in some specific circumstance (such as abscesses)

Prostatitis- 500 mg twice daily to 750 mg twice daily for 2 to 4 weeks (acute) to 4 to 6 weeks (chrocin)

Elderly patients
Elderly 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

In patients with impaired liver function no dose adjustment is required

Method of administration
For oral 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 excipients listed in section 6.1. Concomitant administration of ciprofloxacin and tizanidine.

4.4 Special warnings and precautions for use

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 uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-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 consider the local prevalence of resistance in Escherichia colito 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 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' diarrhea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited. Infections of the bones and joints Ciprofloxacin should be used in combination with other antimicrobial agents depending on the 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 weightbearing joints of immature animals. Safety data from a randomized 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. Bronchopulmonary 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 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 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 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 severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin. Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids. 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 exacerbated.

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.

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. Psychiatric reactions may occur even after 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. 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.

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 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 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 Cmaxand AUC of ciprofloxacin

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 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 drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with (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 the 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 (lifethreatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide	Mania, incl. hypomania

			ideations/thoughts or suicide attempts and completed suicide) Hallucinations	attempts and completed suicide)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri)	Peripheral neuropathy and polyneuropathy
Eye Disorders		Visual disturbances (e.g. diplopia)	Visual colour distortions		

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, 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: Antibiotics, ATC code:

J01MA02

Mechanism of Action
As a fluoroquinolone 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.

Pharmacokinetic/pharmacodynamic 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 multiple 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 susceptibility to fluoroquinolones, which depends on the 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.

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 concentrations increase proportionately with doses up to 1000 mg. The absolute bioavailability is approximately 70-80%.

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 (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

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.

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 or phototumorigenic effect of ciprofloxacin in-vitro and inanimal 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 excipients

Microcrystalline Cellulose
Croscarmellose Sodium BP
Crospovidone BP
Magnesium stearate
Methylene Chloride BP
Purified Talc BP
Sodium starch glycolate BP
Starch BP
Colloidal Silicon Dioxide
Purified water BP

Film-coat
Instacoat White Aqueous (IA-III-4001) I.H

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Alu – Alu Blister pack of 1 x 10 Tablets in a carton

6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 APPLICANT AND MANUFACTURER

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