SUMMARY OF PRODUCT CHARACTERISTICS[SmPC]

1.0 NAME OF THE MEDICINAL PRODUCT

Ciprovam Tablet BP 500mg

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contain Ciprofloxacin Hydrochloride

List of Excipients
Corn starch (67.26mg), Microcrystalline (17.46mg), Talc powder (5.76mg), Sodium starch (5.76mg), Magnesium stearate (9.06mg), Methylparaben (3.43mg) and Propylparaben (0.69mg).

3.0 PHARMACEUTICAL FORM

An off white biconvex shaped caplet with CIPROVAM 500 on one side and TL on other side.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ciprovam tablets are indicated for the treatment of the following infections

Adults

• Lower Respiratory tract infections due to Gram-negative bacteria

- Pneumonia

- Exacerbations of chronic obstructive pulmonary disease

- Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

• Chronic suppurative otitis media

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

• Urinary tract infections

• 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 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

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 ciprovam 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 coadministration with other appropriate antibacterial agents depending on the pathogens involved.

Adult

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

Genital tract infections	Gonococcal uretritis and cervicitis	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
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 Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and		500 mg twice	7 to 14 days

soft tissue	daily to 750 mg twice daily	
Bone and joint infections	500 mg twice daily to 750 mg twice daily	Max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance	500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria 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 exposure	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Elderly patients

Elderly patients should receive a dose selected according to the severity of the infection and the patient's 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 m 2]**	**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

Method of Administration

Oral administration

4.3 Contraindications

Hypersensitivity to the active substance or other quinolones or to any of the excipients used. Concomitant administration of Probenecid, Metoclopramide, Omeprazole, Agomelatine,

Zolpidem, Methotrexate, Theophylline, Phenytoin, tizanidine etc

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ciprovam is not recommended for the treatment of Streptococcal infections due to inadequate efficacy. *Severe infections and mixed infections with Gram-positive and anaerobic pathogens* Ciprovam monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprovam must be co-administered with other appropriate antibacterial agents.

Genital tract infections

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

Therefore, ciprovam 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 ciprovam should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded based on local prevalence data. 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 ciprovam that may be used in uncomplicated cystitis in premenopausal 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 to the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

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

Travellers' diarrhoea

The choice of ciprovam should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints

Ciprovam 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. Treatment should be initiated only after a careful benefit/ risk evalulation, due to possible adverse events related to joints and/ or surrounding tissue. 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 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

Ciprovam 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 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

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.

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.

Hypoglycemia

As with other quinolones, hypoglycemia 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 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 super infection. 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.

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

Drugs known to prolong QT interval Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics). Chelation complex formation The simultaneous administration of ciprovam (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 ciprovam. Consequently, ciprovam 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 ciprovam should be avoided because absorption of ciprovam may be reduced. Probenecid interferes with renal secretion of ciprovam. Co-administration of probenecid and ciprovam 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 ciprovam on other medicinal products:

Tizanidine

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 ciprovam Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

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.

Zolpidem

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

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.

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 anti-coagulant 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 normalised ratio) is difficult to assess. 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.

4.6 ADVERSE REACTIONS

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency is listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**	**Rare ≥ 1/10 000 to < 1/1 000**	**Very Rare < 1/10 000**	**Frequency not known (cannot be estimated from available data)**
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (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	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia, Hypoglycemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (Potentially culminating in suicidal ideations/thoug hts or suicide attempts and completed suicide) Hallucinations	Psychotic reactions (Potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)	Mania, hypomania
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par and Dysaesthesia Hypoesthesia Tremor Seizures (Including status epilepticus Vertigo	Migraine Disturbed coordinationGait disturbance Olfactory nerve disorders Intracranial hypertension Pseudotumor cerebri	Peripheral neuropathy and polyneuropathy

Eye Disorders			Visual disturbances (e.g. Diplopia)	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and torsades de pointes (Reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (Including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastro intestinal and abdominal pains Dyspepsia		Pancreatitis	

		Flatulence			
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 syndrome (Potentially life threatening) Toxic epidermal necrolysis (Potentially life threatening)	Acute generalised exanthematous pustulosis (AGEP) DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome)
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 Tubulointerstiti -al 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

4.7 OVERDOSES

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Ciprofloxacin is a broad-spectrum anti-infective agent of the fluoroquinolone class. Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, strand supercoiling repair, and recombination.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of single doses of 500 mg of ciprovam caplets, 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%. A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 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 (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

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

	Oral administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M1- M4)	11.3	7.5

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

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch, Microcrystalline, Talc powder, Sodium starch, Magnesium stearate, Methylparaben and Propylparaben.

6.2 SHELF-LIFE

3 Years.

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in a dry place.

6.4 NATURE AND CONTENTS OF CONTAINER

Allu-Allu blister pack containing 10 tablets placed in a printed carton.

6.5 Pack sizes:

10 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements for disposal

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

7.0 APPLICANT /MANUFACTURER

Tuyil Pharmaceutical Industries Limited,
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Nigeria
Tel: 08033565739
Email: tuyilmanagement@yahoo.com