BRAND NAME:	**OSYCIPRO TABLETS**
GENERIC NAME:	**CIPROFLOXACIN TABLETS USP 500 MG**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**OSYCIPRO TABLETS**
GENERIC NAME:	**CIPROFLOXACIN TABLETS USP 500 MG**

1. Name of drug product

OSYCIPRO TABLETS

1.1 (Trade) name of product

OSYCIPRO TABLETS

(Ciprofloxacin Tablets USP 500 mg)

1.2 Strength

Ciprofloxacin Hydrochloride 500 mg

1.3 Pharmaceutical Dosage Form

Oral dosage form **(**Tablets)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each film coated tablets contains:

Ciprofloxacin Hydrochloride USP

Equivalent to Ciprofloxacin …….500 mg

Excipients……..q.s.

Color: Titanium dioxide

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Batch Formula:

Batch Size: 423.000 Kg ≅ 7,50,000 Tablets

Sr. No.	Ingredients	Spec	Unit Formula (mg)	Batch Formula (kg)
GRANULATION				
DRY MIXING				
1	Ciprofloxacin Hydrochloride* Eq. to Ciprofloxacin	USP	140.483	105.362*
2	Maize Starch	BP	200.467	157.867***
3	Lactose	BP	138.750	104.062 **
BINDER				
4	Maize Starch	BP	29.000	21.75
5	PVP K-30	B8	5.000	3.75
6	Sodium Benzoate	BP	0.800	0.600
7	Purified water	IH	q.s.	66.000
LUBRICATION				
8	Talcum	BP	6.250	4.687
9	Colloidal Anhydrous Silica (Aerosil)	BP	5.000	3.75
10	Sodium Starch Glycolate	BP	14.750	11.062
11	Magnesium Stearate	BP	9.500	7.125
Weigh of Compressed Tablet			**550.00**	
COATING				
12	Insta Coat Universal (Blue – A05R01852)	IH	1.000	10.50
13	Purified water	IH	q.s.	67.50
Weigh of Coated Tablet			**564.000**	**423.00 kgs**

Remark:

*Erythromycin Stearate Calculation :(Std.Qty mentioned above (392.000 kg) is with respect to potency 63.77%). Actual Quantity of Erythromycin Stearate will be taken after calculation based on potency.

**Maize Starch quantity changes according to change in quantity of Erythromycin Stearate.

***10% Extra Insta Coat Universal (IC-U-1308) white added to compensate the loss of material during coating Process w added in formulation to compensate loss during coating process.

MAXHEAL For Maximum Healing	
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3. PHARMACEUTICAL DOSAGE FORM

Tablets

White oval shape, film coated tablets, debossed 'CIPRO 500' on one side and "MAXHEAL" on other side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin 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.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - pneumonia
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negativebacteria
- Acute pyelonephritis
- Complicated urinary tract infections
- Bacterial prostatitis
- Genital tract infections
  - gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae
  - epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae

pelvic inflammatory disease including cases due to susceptible Neisseriagonorrhoeae

- 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.

In exacerbations of chronic obstructive pulmonary disease Ciprofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

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

Children and adolescents

- Broncho-pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis
- Complicated urinary tract infections and acute pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

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

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

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:

• *Infections of the Upper & lower respiratory tract:*

Daily dose in mg: 500 mg twice daily to 750 mg twice daily

Total Duration : 7 to 14 days

• *Malignant external otitis (in Upper respiratory tract):*

Daily dose in mg: 750 mg twice daily

Total Duration : 28 days upto 3 months

• ***Urinary tract infections:***

• *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:*

Daily dose in mg : 500 mg twice daily to 750 mg twice daily

Total Duration : at least 10 days, it can be continued for longer than 21 days in somespecific circumstances (such as abscesses)

• *Prostatitis*:

Daily dose in mg: 500 mg twice daily to 750 mg twice daily

Total Duration: 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 twicedaily (at least 14 days)

• ***Infections of the gastro-intestinal tract and intra-abdominal infections***

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• *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 (for 1 day)

• *Diarrhoea caused by Shigella dysenteriae type 1:* 500 mg twice daily (for 1 day)

• *Diarrhoea caused by Vibrio cholerae:* 500 mg twice daily (for 5 day)

• *Typhoid fever:* 500 mg twice daily (for 7 day)

• *Intra-abdominal infections due to Gram-negative bacteria:* 500 mg twice daily to 750 mgtwice daily (for 5 to 14 days)

• ***Infections of the skin and soft tissue:***

Daily dose in mg: 500 mg twice daily to 750 mg twice daily

Total Duration: 7 to 14 days

• ***Bone and joint infections***

Daily dose in mg: 500 mg twice daily to 750 mg twice daily

Total Duration: max 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.***

Daily dose in mg: 500 mg twice daily to 750 mg twice daily

Total Duration: Therapy should be continued over the entire period of neutropenia

• ***Prophylaxis of invasive infections due to Neisseria meningitides***

Daily dose in mg: 500 mg as a single dose

Total Duration: 1 day (single dose)

• ***Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able toreceive treatment by oral route when clinically appropriate.***

Drug administration should begin as soon as possible after suspected or confirmed exposure.

Daily dose in mg: 500 mg twice daily

Total Duration: 60 days from the confirmation of Bacillus anthra

Paediatric population

• ***Cystic fibrosis:***

Daily dose in mg: 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.

Total Duration: 10 to 14 days

•***Complicated urinary tract infections and pyelonephritis:***

Daily dose in mg: 10 mg/kg body weight twice daily to 20 mg/kg body weight twice dailywith a maximum of 750 mg per dose.

Total Duration: 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:***

Daily dose in mg: 10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.

Total Duration: 60 days from the confirmation of Bacillus anthracis exposure

• ***Other severe infections:***

Daily dose in mg: 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.

Total Duration: 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 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

For oral use.

Ciprofloxacin Tablet 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 or mineral-fortified fruit-juice.

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

4.4 Special warnings and 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. Treatmentof 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 multiple, bodysystems (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 serious 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 mustbe 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 shouldonly 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 quinolones.

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 treatmentduration. This is all the more to be taken into account as regards the increasing resistancelevel 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 datatogether 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 experiencedin 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 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 significantbetween groups. Treatment should be initiated only after a careful benefit/risk evaluation, dueto 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.

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 tendondisease/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

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. immobilization). 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.

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 occurciprofloxacin should be discontinued. Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidalideations/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 paranesthesia, hyperesthesia, 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.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic 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 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system

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

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudomonas species.

Cytochrome P450

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

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

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

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

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

4.5 Interaction with other 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 QT interval.

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 Cmax and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:

Agomelatine: In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting ina 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

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) whengiven concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

Theophylline: Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline- induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives: On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivativeswere 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 Kantagonist 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 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 1A2isozyme, 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 for7 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 the benefits.

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 womenindicates no malformative or feto/neonatal toxicity of ciprofloxacin. As a precautionarymeasure, 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.

The frequencies of adverse reactions are ranked according to the following convention. The frequency grouping is defined using the following convention: Common (≥1/100 to <1/10);

Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Frequency not known (cannot be estimated from available data)

Infections and infestations

Uncommon : Mycotic superinfections

Blood and lymphatic system disorders

Uncommon : Eosinophilia

Rare : Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia,and Thrombocytaemia

Very Rare : Haemolytic anemia, Agranulocytosis, Pancytopenia (lifethreatening), Bone marrow depression (life threatening)

Endocrine disorders

Not known : Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Metabolism and nutrition disorder

Uncommon : Decreased appetite

Rare : Hyperglycaemia, Hypoglycaemia, Hypoglycaemic coma

Psychiatric disorders

Uncommon : Psychomotor hyperactivity / agitation

Rare : Confusion and disorientation Anxiety reaction abnormal dreams depression,Halucinations.

Very Rare : Psychotic reactionsNot Known : Mania

Nervous system disorders

Uncommon : Dizziness, headache, Sleep disorder & Taste disorder

Rare : Par- and Dysaesthesia, Hypoaesthesia, Tremor, Seizures

Very Rare : Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri

Not known : Peripheral neuropathy and polyneuropathy

Eye disorders

Rare : Visual disturbunces

Very rare : Visual colour distortions

Ear and labyrinth disorders

Rare : Hearing loss/impaired, tinnitus

Cardiac disorders

Rare : Tachycardia

Not known : ventricular arrhythmia and torsades de pointes, ECG QT prolonged

Vascular disorders

Rare : Vasodilation, Hypotension, SyncopeVery rare : Vasculitis

Respiratory, Thoracic and Mediastinal Disorders

Rare : Dyspnoea

Gastrointestinal disorders

Common : Diarrhoea, nausea

Uncommon : Vomiting, dyspepsia, gastrointestinal abdominal pain, FlatulenceRare : Antibiotic associated colitis, possible fat

Very Rare : Pancreatitis

Hepatobiliary disorders

Uncommon : Increase in transaminases increase bilirubin

Rare : Hepatic impairment, Cholestatic icterus, HepatitisVery rare: Liver necrosis

Skin and subcutaneous tissue disorders

Uncommon : Pruritus and rash, urticarial

Rare : Photosensitivity reactions

Very Rare : Petechiae, Erythema multiforme, Erythema nodosum, Stevens - Johnson syndrome, Toxic epidermal necrolysis.

Not known : Acute generalised exanthematous pustulosis, Drug reaction with Eosinopphilia and systemic symptoms

Musculoskeletal and connective tissue disorders

Uncommon : Musculoskeletal pain, Arthralgia

Rare : Myalgia, arthritis, increased muscles tone and cramping

Very rare : Muscular weakness, Tendinitis, Tendon rupture, Exacerbation of symptoms of myasthenia gravis

Renal and urinary disorders

Uncommon : Renal impairment

Rare : Renal failure, Tubulointerstitial nephritis, Crystalluria

General disorders and administration site.

Uncommon : Fever, asthenia

Rare : Oedema, Sweating

Investigations

Uncommon : Increased in blood alkaline phosphataseRare : Increased amylase

Not Known : International normalized ratio increased

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 reportedto cause acute renal failure.

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

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

5.0 Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Fluoroquinolones.ATC Code: J01MA02.

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

Pharmacokinetic /Pharmacodynamic relationship:

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

5.2 Pharmacokinetic properties

Absorption: 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 largelyin 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 clinicallyrelevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin in-vitro and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight- bearing joints in 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

BRAND NAME:	**OSYCIPRO TABLETS**
GENERIC NAME:	**CIPROFLOXACIN TABLETS USP 500 MG**

6. Pharmaceutical Particulars

6.1. List of excipients

Microcrystalline Cellulose

Lactose

Croscarmellose Sodium

Maize Starch

Purified Talc

Sodium Starch glycolate

Colloidal anhydrous silica

Magnesium Stearate

Insta-Coat Universal

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below 30°C, Protect from light.

Keep this medicine out of the sight and reach of children.

6.5. Nature and contents of container

10 x 1 x 10 Tablets pack in Alu-Alu blister pack

6.6. Instruction for use and handling

No special requirement

7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT

GUJARAT-394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.