1.5 PRODUCT INFORMATION

1.5.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARACTERISTICS)

1. Name of the finished pharmaceutical product

CIPROGLAX [Ciprofloxacin Tablets USP 500 mg]
Strength **:** 500 mg
Pharmaceutical Form **:** Tablet

2. Qualitative and quantitative composition

Each film coated tablet contains:
Ciprofloxacin HCl USP
Equivalent to Ciprofloxacin….500 mg
Excipients .....q.s.
Colour: Titanium Dioxide

3. Pharmaceutical form

Film-coated tablet

White coloured, oblong, biconvex film-coated tablets having a break line mark on one side and plain on other side of each tablet.

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin is indicated for the treatment of a wide variety of infections caused by susceptible gram-positive and gram-negative organisms.
Including mixed infections caused by two or more organisms. It may also be used for infections caused by multi drug resistant bacteria.
Ciprofloxacin is indicated for the treatment of the following infections caused by susceptible bacteria:

- Respiratory Tract Infections: Pneumonia, bronchopneumonia, infected pleuris, emphysema, lung abscess, infected bronchiolitis, acute exacerbation of chronic bronchitis and lung infections in patients with cystic fibrosis.
- Urinary Tract Infections: Acute and chronic pyelonephritis, prostatitis, cystitis, epididymitis and chronic complicated or recurrent UTI.
- E.N.T.: Otitis media, sinusitis, mastoiditis.
- Gonorrhoea: Including urethral, rectal and pharyngeal gonococcal infections and even those caused by resistant gonococci.
- Skin and Soft Tissue Infections: Infected ulcers, wound infections, abscesses, cellulitis, otitis externa, infected burns.
- Gastrointestinal Tract Infections: Enteric fever, bacterial diarrhoeas.
- Intra-Abdominal Infections: Peritonitis, intra-abdominal abscess, cholangitis, choleocystitis.
- Gynaecological Infections: Salpingitis endometritis, pelvic inflammatory disease.
- Bone and Joint Infections: Acute and chronic osteomyelitis, septic arthritis.
- Severe systemic Infections: Septicemia, bacteremia and infection in immuno compromised patients.

4.2 Posology and method of administration

The Dosage of Ciprofloxacin is determined on the basis of severity of infection, type of infecting organisms and age, weight and renal function of the patient.
The recommended dosage schedule of oral Ciprofloxacin is as follows:

- Uncomplicated UTI: 250 mg every 12 hours.
- Prostatitis and complicated UTI in patients with severe-underlying structural abnormalities: 500 mg every 12 hours.
- Lower respiratory tract infections: Mild-250 mg, moderate to severe-500 mg every 12 hours. Dosage of 750 mg every 12 hours should preferably be used in cases of infection with resistant gram-positive bacteria.
- ENT infections: 500 to 750 mg every 12 hours.
- Bone and joint infections: 500 to 750 mg every 12 hours.
- Gastroenteritis: 250 mg every 12 hours.
- Enteric fever: 500 mg every 12 hours.
- Gynecological infections: 500 mg every 12 hours.
- Gonorrhoea: 250 mg single dose.
- Septicemia, bacteremia and intra-abdominal infections: Initial IV Ciprofloxacin therapy may be followed by oral Ciprofloxacin 500 to 750 mg every 12 hours.

The total daily dosage should be halved in patients with severe renal impairment.
Administrations:
Ciprofloxacin may be administered independently of meals. However, for better bio-availability, it should preferably be taken on an empty stomach.
Concurrent use of antacids should be avoided.
Patients should be instructed to drink fluids liberally during Ciprofloxacin therapy.

4.3 Contraindications

Ciprofloxacin is contraindicated in individuals with a history of hypersensitivity to Ciprofloxacin or any other quinolone derivative.
Ciprofloxacin has been shown to cause arthropathy in weight bearing joints of immature animals. Though the relevance of this to humans is unknown, it's use in children and adolescents is not recommended.

4.4 Special warnings and special precautions for use

As Ciprofloxacin may cause CNS stimulation, it should be used with caution in patients with CNS disorders such as severe cerebral arteriosclerosis or epilepsy.
Patients receiving this drug should be well hydrated to prevent crystalluria.
Excessive aIkalinization of urine should be avoided. The dosage should be reduced in patients with renal impairment.
Reproduction studies in animals at doses up to 6 times the usual daily human dose have not revealed any evidence of impaired fertility or teratogenicity due to Ciprofloxacin.
However information from well controlled studies in pregnant women is not available. Since Ciprofloxacin causes arthropathy in immature animals. It should not be used in pregnant and nursing women.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin

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

Ciprofloxacin like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, and antipsychotics).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminum, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1 – 2 hours before or at least 4 hours after the preparation.

The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Coadministration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

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

Theophylline

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

Other xanthine derivatives

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

Phenytoin

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

Cyclosporin

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

Vitamin K antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after Coadministration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

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 C_{max} and AUCof ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after coadministration with ciprofloxacin.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31% respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil

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

Zolpidem

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

4.6 Fertility, pregnancy and lactation

Ciprofloxacin has been shown to cause arthropathy in immature animals, and therefore its use during pregnancy is not recommended.

Studies have indicated that Ciprofloxacin is secreted in breast milk.

Administration to nursing mothers is thus not recommended.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

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

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

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Very Rare** < 1/10,000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections			
Blood and 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) (see section 4.4) Serum sickness like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia (see section 4.4)		

Psychiatric disorders		Psychomotor hyperactivity/agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideation/thoughts or suicide attempts and completed suicide) Hallucination	Psychotic reactions (potentially culminating in suicidal ideations/thought or suicide attempts and completed suicide)	Mania, hypomania
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epliepticus Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and psuedotumor cerebri	Peripheral neuropathy and polyneuropathy
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss/ Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation) ECG QT prolonged (see section 4.4 and 4.9)
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		

Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence	Antibiotic associated diarrhoea including pseudomembraneous colitis (very rarely with possible fatal outcome)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions	Petechial Erythema multiform Erythema nodosum Stevens-Johnson syndrome (potentially life threatening) Toxic epidermal necrolysis (potentially life threatening)	Acute generalized exanthematous pustulosis (AGEP), DRESS
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in

					patients treated with Vitamin K antagonists)

Paediatric patients

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

4.9 Overdose

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg or Ca-containing antacids which reduce the absorption of Ciprofloxacin.

Only a small amount of Ciprofloxacin (<10%) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The antibacterial spectrum of Ciprofloxacin includes Gram-negative and Gram-positive organisms viz. Acinetobacter, Aeromonas, Campylobacter jejuni, Citrobacter freundii, Citrobacter species, Corynebacterium, Edwardsiella, Enterobacter cloacae, Enterobacter species, Listeria, Morganella morganii, E.coli, Klebsiella spp., Salmonella enteritidis., P. mirabilis, P. vulgaris, Yersinia, Ps. aeruginosa, Shigella flexneri, Shigella sonnei, Hafnia, H. influenzae, H. para-influenzae, N. gonorrhoeae, M. catarrhalis, Vibrio, Staph. aureus (including methicillin resistant strains), Staph. epidermidis, Strep. pyogenes, Strep. species, Brucella, Pasteurella, Plesiomonas, Providencia rettgeri, Providencia stuartii, Serratia marcescens.
In vitro sensitivity does not necessarily imply in vivo efficacy.

The following organisms show varying degrees of in vitro sensitivity to Ciprofloxacin:
Alcaligenes, Enterococcus faecalis, Flavobacterium, Gardnerella, Legionella, Mycobacterium fortuitum, Mycobacterium tuberculosis, Mycoplasma hominis, Streptococcus agalactiae, Chlamydia.

The following are usually resistant:

- Enterococcus faecium, Ureaplasma urealyticum, Nocardia asteroides.
- Moderately sensitive organisms:
- Anaerobes (Peptococcus, Peptostreptococcus).
- Moderately resistant organisms:
- Bacteriodes, Treponema pallidium.

Pharmacotherapeutic group: Fluoroquinolones

5.2 Pharmacokinetic properties

Ciprofloxacin is well absorbed when given orally with a bioavailability of 70%. The mean peak plasma concentrations achieved after oral administration of 250 mg, 500 mg and 750 mg of

Ciprofloxacin are 1.2 mcg/mL, 2.4 mcg/mL and 4.3 mcg/mL respectively, achieved within 1-2 hours of administration. Absorption is delayed when Ciprofloxacin is given with a meal. Plasma protein binding ranges from 20 to 40%.
Ciprofloxacin is widely distributed throughout the body viz. lung, skin, fat, muscle, cartilage, bone and genital tissues including the prostate. It is present in active form in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile and prostatic secretions.
Ciprofloxacin is partly metabolized in the liver. About 50% of an oral dose is recovered unchanged in the urine and 15% as active metabolites viz. oxociprofloxacin. The rest undergoes biliary excretion and transluminal secretion across the intestinal mucosa.
The plasma elimination half-life is about 3.5 - 4.5 hrs. The half-life may be prolonged in severe renal insufficiency and in the elderly.

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 in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. Pharmaceutical particulars

6.1 List of excipients
Lactose
Microcrystalline cellulose
Starch (maize)
Purified water
Purified Talc
Colloidal Silicon dioxide
Sodium starch Glycolate
AC-DI-SOL (Crosscarmellose Sodium)
Magnesium Stearate
P.V.P.K. 30
Titanium Dioxide
P.E.G 6000
Hydroxy propyl methyl cellulose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30 °C. Protect from light.

6.5 Nature and contents of container
Box of 1 × 10 Tablets,
Box of 10 × 10 Tablets,
Box of 100 × 10 Tablets,
Jar of 100, 500 & 1000 Tablets.

6.6 Special precautions for disposal and other handling
Keep all the medicines away from reach of children.

7. Marketing authorisation holder and Manufacturing site address

UMEDICA LABORATORIES PVT. LTD.
302, Dalamal House, Jamnalal Bajaj Road,
Nariman Point, Mumbai – 400021.
Tel No. (022)62455050/40028503
Email: regn_ho@umedicalabs.com

Manufacturing Address:
Umedica Laboratories Pvt. Ltd.,
Plot No. 221, G.I.D.C.,
VAPI - 396 195, Dist. Valsad,
GUJARAT
Country: INDIA

8. Marketing authorization number
NA

9. Date of first <Registration> / Renewal Of The <Registration>
NA

10. Date of revision of the text
20/05/2020