For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Ciprofloxacin Hydrochloride Tablets IP
(Brand Name: CEBRAN® 250 / 500 Tablets)

WARNING
Fluoroquinolones, including ciprofloxacin have been associated with disabling and potentially irreversible serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of myasthenia gravis. Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.
Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

2. Qualitative and Quantitative Composition

Each Film-Coated Tablet Contains:
Ciprofloxacin Hydrochloride IP equivalent to Ciprofloxacin ……. 250 mg / 500 mg.
Excipients ……. q.s.
Approved Colour : Titanium Dioxide IP

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Ciprofloxacin 250 mg and 500 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

CEBRAN Tablets are indicated in the treatment of various bacterial infections such as acute sinusitis, respiratory tract infections, urinary tract infections, infectious diarrhea, skin and skin structure infections, intra-abdominal infections, typhoid fever, chronic prostatitis, and gonorrhoea.

4.2Posology and Method of Administration

For oral administration in adults only.
CEBRAN Tablets are usually recommended in a dose of 250 to 500 mg twice daily.
Ciprofloxacin is administered as per following dosing schedule for the treatment of infections when caused by susceptible strains of the microorganisms:

- Acute sinusitis: 500 mg twice daily.

- Respiratory tract infections: 250 to 750 mg twice daily.
- Urinary tract infections: 250 to 500 mg twice daily.
- Infectious diarrhea: 500 mg twice daily.
- Skin and skin structure infections: 500 to 750 mg twice daily.
- Intra-abdominal infections: 500 mg twice daily.
- Typhoid fever: 500 mg twice daily.
- Chronic prostatitis: 500 mg twice daily for 28 days.
- Gonorrhoea: 500 mg as a single dose.
- Pseudomonal lower respiratory tract infection in cystic fibrosis: 750 mg twice daily.

In renal impairment, the dosing regimen is 250 to 500 mg every 12 hours, every 18 hours or every 24 hours depending on whether creatinine clearance is 30 to 50 ml/min, 5 to 29 ml/min, or if patients are on hemodialysis or peritoneal dialysis, respectively.
The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required.
CEBRAN Tablets may be administered with or without food. The tablet should be swallowed whole with water and not to be cut, crushed or chewed.
Or, as prescribed by the physician.

4.3Contraindications

CEBRAN Tablets are contraindicated in the following:

- Known or suspected hypersensitivity to ciprofloxacin/other quinolones or to any component of the formulation.
- Concomitant administration with tizanidine and theophylline.
- In patients with a history of tendon disorders related to quinolone use.

4.4Special Warnings and Precautions for Use

Caution - Safety Issues with Fluoroquinolone Antibiotics: The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class are:

- Disturbances in attention.
- Disorientation.
- Agitation.
- Nervousness.
- Memory impairment.
- Serious disturbances in mental abilities called delirium.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had

a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Photosensitivity/Phototoxicity: Moderate to severe photosensitivity/phototoxicity reactions can be associated with the use of quinolones after sun or UV light exposure. Phototoxicity may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands). Drug therapy should be discontinued if phototoxicity occurs.

Tendinopathy and Tendon Rupture: Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Inflammation and tendon rupture can occur, sometimes bilaterally, even within the first 48 hours, during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin should be used with caution in patients with a history of tendon disorders, and should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.

Exacerbation of Myasthenia Gravis: Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

Central Nervous System (CNS) Effects: Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin may also cause CNS events including dizziness, confusion, tremors, hallucinations, depression, and, rarely, psychotic reactions have progressed to suicidal ideations/thoughts and self-injurious behavior such as attempted or completed suicide. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued, patients should be advised to inform their healthcare provider immediately and appropriate measures instituted. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. As with all fluoroquinolones, ciprofloxacin should be used with caution in epileptic patients and patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g., cerebral arteriosclerosis, previous history of convulsion, reduced cerebral blood flow, altered brain structure, or stroke), or in the presence

of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction).

***Clostridium Difficile*-Associated Diarrhea (CDAD):** *Clostridium difficile*-associated diarrhea has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

Peripheral Neuropathy: Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Symptoms may occur soon after initiation of ciprofloxacin and may be irreversible. Ciprofloxacin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation.

Prolongation of the QT Interval: Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of *torsade de pointes* have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin should be avoided in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (e.g., congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (e.g., quinidine, procainamide), or Class III antiarrhythmic agents (e.g., amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Other Serious and Sometimes Fatal Reactions: Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- Fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome).
- Vasculitis; arthralgia; myalgia; serum sickness.
- Allergic pneumonitis.
- Interstitial nephritis; acute renal insufficiency or failure.
- Hepatitis; jaundice; acute hepatic necrosis or failure.

- Anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Syphilis: Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

General: Crystals of ciprofloxacin have been observed in the urine of laboratory animals, which is usually alkaline. Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

4.5Drug Interactions

Tizanidine: In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg twice daily for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

Theophylline: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Other Xanthine Derivatives: Some quinolones, including ciprofloxacin, have been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life. On concurrent administration of ciprofloxacin and caffeine or pentoxifylline containing products, elevated serum concentrations of these xanthine derivatives were reported.

Chelation Complex Formation: Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminium antacids, polymeric phosphate binders (e.g., sevelamer, lanthanum carbonate), sucralfate, didanosine, or other highly buffered drugs or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired.

Omeprazole: Concomitant administration of a single dose of ciprofloxacin 500 mg tablet and once-daily administration of 20 mg omeprazole pretreatment for 4 days resulted in a 16% reduction of mean C_{max} and mean AUC of ciprofloxacin.

Phenytoin: Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related undesirable effects when ciprofloxacin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of ciprofloxacin with phenytoin.

Oral Antidiabetic Agents: Hypoglycemia has been reported when ciprofloxacin and oral antidiabetic agents (mainly sulfonylureas e.g., glyburide, glimepiride) were co-administered, presumably by intensifying the action of the oral antidiabetic agent. The concomitant administration of ciprofloxacin with glyburide has resulted in severe hypoglycemia (rare occasions). Fatalities have been reported.

Cyclosporine: Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Oral Anti-coagulants: Simultaneous administration of ciprofloxacin with an oral anticoagulant may augment the effect of the anticoagulant. 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 international normalized ratio (INR) is difficult to assess. Prothrombin time and INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (e.g., warfarin).

Probenecid: Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum.

Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions.

Metoclopramide: Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

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 a 5-fold increase in mean AUC and a 2.5-fold increase in mean C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs (but not acetyl salicylic acid) in combination with very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

Ropinirole: In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with 500 mg ciprofloxacin twice-daily, the mean C_{max} and mean AUC of ropinirole were increased by 60% and 84%, respectively. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin.

Lidocaine: In a study conducted in 9 healthy volunteers, concomitant use of 1.5 mg/kg i.v. lidocaine with 500 mg ciprofloxacin twice daily resulted in an increase of lidocaine C_{max} and AUC by 12% and 26%, respectively. Although lidocaine treatment was well tolerated at this

elevated exposure, a possible interaction with ciprofloxacin and an increase in side effects related to lidocaine may occur upon concomitant administration.

Clozapine: Following concomitant administration of 250 mg ciprofloxacin with 304 mg clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Careful monitoring of clozapine and olanzapine associated adverse effects and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil: Following concomitant administration of a single oral dose of 50 mg sildenafil with 500 mg ciprofloxacin to healthy subjects, the mean C_{max} and mean AUC of sildenafil were both increased approximately two-fold. Therefore, sildenafil should be used with caution when co-administered with ciprofloxacin.

Drugs Known to Prolong QT Interval: Precaution should be taken when using ciprofloxacin concomitantly with drugs known to prolong the QT interval (e.g., class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) as ciprofloxacin may have an additive effect on the QT interval.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C. There are no adequate and well controlled studies in pregnant women. In animal studies ciprofloxacin does not appear to be teratogenic, but it may damage developing cartilage. There are insufficient data to recommend the use of ciprofloxacin in pregnancy.

Lactating Women

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug therapy, taking into account the importance of the drug to the mother.

Paediatric Patients

Quinolones cause arthropathy in the weight bearing joints of immature animals and are therefore generally not recommended in children and growing adolescents. CEBRAN Tablets are contraindicated for use in paediatric patients.

Geriatric Patients

Geriatric patients are at increased risk for developing tendon disorders, including tendon rupture when being treated with a fluoroquinolone such as ciprofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Caution should be used when prescribing ciprofloxacin to elderly patients especially those on corticosteroids.

Renal Impairment Patients

Alteration of the dosage regimen is necessary for patients with impairment of renal function. Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also

metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

4.7Effect on Ability to Drive and Use Machines

Ciprofloxacin may cause dizziness and impair performance of skilled tasks like driving, and use of machines. These effects also enhanced by alcohol. So it is not advisable to drive or operate machinery for several hours after taking this medication.

4.8Undesirable Effects

Clinical Trials Experience

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

The most frequently reported drug-related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), abnormal liver function tests (1.3%), vomiting (1%), and rash (1%).

Additional medically important events that occurred in less than 1% of ciprofloxacin patients are listed below:

Body as a whole: Headache, abdominal pain/discomfort, foot pain, pain in extremities.

Cardiovascular: Palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension.

Central nervous system: Restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures (including status epilepticus), grand mal convulsion, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide), paresthesia, abnormal gait.

Gastrointestinal: Painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, hepatitis.

Lymphatic: Lymphadenopathy, petechial.

Metabolic: Increase in amylase and lipase, hyperglycemia, hypoglycemia.

Musculoskeletal: Arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout, muscle weakness.

Renal: Nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain.

Respiratory: Dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

Skin/Hypersensitivity: Allergic reaction, pruritus, urticaria, photosensitivity/phototoxicity reaction, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating.

Special senses: Blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia.

Post-Marketing Experience

The following adverse events have been reported for fluoroquinolones post-approval. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute generalized exanthematous pustulosis (AGEP), agitation, agranulocytosis, albuminuria, anaphylactic reactions (including life-threatening anaphylactic shock), anosmia, candiduria, cholesterol elevation, confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation, hemolytic anemia, hepatic failure (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), International Normalized Ratio (INR) increased (in patients treated with Vitamin K antagonists), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, exacerbation of myasthenia gravis, myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy that may be irreversible, altered serum phenytoin, photosensitivity/phototoxicity reaction, polyneuropathy, elevated serum potassium, prothrombin time prolongation or decrease, pseudomembranous colitis (onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic), QT prolongation, renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation, twitching, vaginal candidiasis, vasculitis and ventricular arrhythmia.

Laboratory Abnormalities

Hepatic: Elevations of ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, serum bilirubin.

Hematologic: Eosinophilia, leukopenia, thrombocytopenia, thrombocytosis, pancytopenia.

Renal: Elevations of serum creatinine, BUN, crystalluria, cylindruria, and hematuria have been reported.

Other: Other changes occurring in less than 0.1% of courses were elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

4.9Overdose

In the event of acute overdose, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function, urinary pH and acidify, if required, to prevent crystalluria and administer magnesium,

aluminium, or calcium-containing antacids to reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

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, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials.

5.2Pharmacodynamic Properties

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic gram-positive microorganisms

- *Enterococcus faecalis* (many strains are only moderately susceptible)
- *Staphylococcus aureus* (methicillin-susceptible strains only)
- *Staphylococcus epidermidis* (methicillin-susceptible strains only)
- *Staphylococcus saprophyticus*
- *Streptococcus pneumoniae* (penicillin-susceptible strains only)
- *Streptococcus pyogenes*

Aerobic gram-negative microorganisms

- *Campylobacter jejuni*
- *Proteus mirabilis*
- *Citrobacter diversus*
- *Proteus vulgaris*
- *Citrobacter freundii*
- *Providencia rettgeri*
- *Enterobacter cloacae*
- *Providencia stuartii*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Haemophilus influenzae*
- *Salmonella typhi*
- *Haemophilus parainfluenzae*
- *Serratia marcescens*
- *Klebsiella pneumoniae*
- *Shigella boydii*

- *Moraxella catarrhalis*
- *Shigella dysenteriae*
- *Morganella morganii*
- *Shigella flexneri*
- *Neisseria gonorrhoeae*
- *Shigella sonnei*

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker.
Ciprofloxacin exhibits *in vitro* minimum inhibitory concentration (MIC) of 1 μg/ml or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Streptococcus pneumoniae* (penicillin-resistant strains only)

Aerobic gram-negative microorganisms

- *Acinetobacter lwoffi*
- *Pasteurella multocida*
- *Aeromonas hydrophila*
- *Salmonella enteritidis*
- *Edwardsiella tarda*
- *Vibrio cholerae*
- *Enterobacter aerogenes*
- *Vibrio parahaemolyticus*
- *Klebsiella oxytoca*
- *Vibrio vulnificus*
- *Legionella pneumophila*
- *Yersinia enterocolitica*

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin same as most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

5.3Pharmacokinetic Properties

Absorption: Ciprofloxacin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption,

however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/ml respectively.

Distribution: After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissues including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humor of the eye.

Metabolism: Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co-administered drug.

Excretion: The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/ml. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/ml. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 l/h which exceeds the normal glomerular filtration rate of 7.2 l/h. Thus, active tubular secretion would seem to play a significant role in its elimination.

6. Nonclinical Properties

6.1 Animal Toxicology

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3-times and 3.5-times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an

additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.
Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single oral doses as low as 5 mg/kg. (approximately 0.07-times the highest recommended therapeutic dose based upon body surface area). After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration (approximately 0.2-times the highest recommended therapeutic dose based upon body surface area).

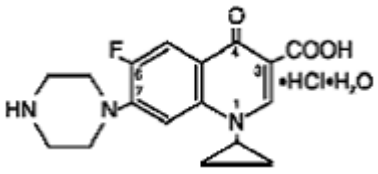
In dogs, ciprofloxacin at 3 mg/kg and 10 mg/kg by rapid intravenous injection (15 seconds) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid intravenous injection also produces hypotension but the effect in this species is inconsistent and less pronounced.
In mice, concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.
Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

7. Description

CEBRAN 250 Tablets are white to off white, circular, biconvex, film coated tablets with engraved ‘CEBRAN - 250’ on one side and plain on other side.
CEBRAN 500 Tablets are white to off white, circular, biconvex, film coated tablets with ‘CEBRAN - 500’ engraved on one side and plain on other side.

CEBRAN 250/500 Tablets contain 250 mg and 500 mg of ciprofloxacin respectively for oral administration in adults.

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibiotic. Ciprofloxacin hydrochloride is a faintly yellowish to light yellow crystalline substance.
Molecular Weight: 385.8 g/mol.
Molecular Formula: C17H18FN3O3 .HCl .H2O
Chemical Name: 1-cyclopropyl-6-fluoro-1,4 dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of CEBRAN 250 & 500 Tablet contain : Microcrystalline Cellulose, Colloidal Silicon Dioxide, Talc, Sodium Starch Glycolate, Magnesium Stearate & Opadry White.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

CEBRAN 250 Tablets: 36 months
CEBRAN 500 Tablets: 36 months

8.3Packaging Information

10 tablets per blister.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30 °C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Patients should be counseled that antibacterial drugs should only be used to treat bacterial infections. Not to use this medicine to treat infections caused by viruses.
- Patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the treatment and increase the likelihood that bacteria will develop resistance to the antibiotic.
- Advise patients that diarrhea may occur with antibacterial drugs which usually end when the antibacterial drug is discontinued.
- Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.
- Instruct patient to drink plenty of fluids while taking this medicine to prevent the formation of highly concentrated urine.
- In case of serious allergic reaction or signs of tendon damage/rupture, discontinue therapy and consult Doctor immediately.
- Dizziness is possible after taking this medicine. Instruct patients not to drive or operate machinery, or do other activities that require mental alertness or coordination until they know how this medicine affects them.

- Instruct patients to avoid sunlight exposure. Therapy should be discontinued if photosensitivity/phototoxicity (sunburn, blisters or swelling of skin, skin eruption) occurs.
- This drug therapy may cause low blood sugar and mental health related side effects. If affected, patient should immediately discontinue therapy and consult Doctor.

10.Details of Manufacturer

Blue Cross Laboratories Pvt. Ltd.
L- 17, Verna Industrial Estate, Verna, Goa – 403 722.

11.Details of Permission or License Number with Date

Cebran 250 Tablet : Manufacturing License No. : 271. Date of product permission : 20/10/1998
Cebran 500 Tablet : Manufacturing License No. : 271. Date of product permission : 20/10/1998

12. Date of Revision

November 2022.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
L-17, VERNA INDUSTRIAL ESTATE, VERNA, GOA - 403 722.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.