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

C-FLOX 250 & 500

(Ciprofloxacin Tablets USP 250 mg & 500 mg)

Composition:
Each tablet contains:
Ciprofloxacin Hydrochloride USP
Equivalent to Ciprofloxacin 250 mg & 500 mg

C-Flox is a broad spectrum and potent synthetic fluoroquinolone antibacterial agent. It is indicated in various respiratory, urinary and other infections caused by susceptible microorganisms.

Clinical Pharmacology:
Ciprofloxacin exhibits potent bactericidal action by interfering with enzyme DNA gyrase which is needed for the synthesis of bacterial DNA. The in vitro antimicrobial spectrum of Ciprofloxacin includes wide range of microorganisms including Gram-negative bacteria like campylobacter jejuni, E. coli, Citrobacters, H. influenzae, H. parainfluenzae, Shigella, Salmonella typhi, Vibrio cholerae, Neisseria gonorrhoea, N. meningitidis, Branhaemella catarrhalis, Kleb. pneumoniae, Brucella melitensis, H.ducrayi, Proteus mirabilis, P.vulgaris, Pseudomonas aeruginosa, Providancia rettgeri, P. startii, Serratia marcescens, Enterobacter cloacae, and Gram-positive bacteria like Staphylococcus aureus, Staph. epidermidis, Staph. haemolyticus, Streptococcus pneumoniae, Streptococcus pyogenes. Most strains of Ps. cepacia, Ps. multophilia and most anaerobic bacteria are resistant to Ciprofloxacin. Ciprofloxacin is slightly less active at acidic pH. Ciprofloxacin does not cross-react with other antimicrobial agents. Synergism is reported with aminoglycosides, clindamycin, metronidazole and particularly beta-lactams. Ciprofloxacin is also shown to have post antibiotic effect (PAE) i.e. continued antibacterial effect after cessation of drug administration.

Ciprofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70% and a peak plasma concentration of about 2.5 mcg per ml is achieved 1 to 2 hours after a dose of 500 mg by mouth. Absorption is delayed in presence of food. Plasma protein binding ranges from 20 to 40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. High concentrations are achieved in bile. The plasma half-life is about 3.5 to 4.5 hours and there is modest accumulation. Half life may be prolonged in severe renal failure. Ciprofloxacin is eliminated principally by urinary excretion and non-renal clearance accounts for one third of its elimination. Urinary excretion is by active tubular secretion and by glomerular filtration. Urinary excretion is reduced by probenecid. At least 4 active metabolites are identified; among which oxociprofloxacin is major urinary metabolite and sulphociprofloxacin the primary fecal metabolite. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as metabolites.

Indications:
C-Flox is indicated for the treatment of the following infections due to sensitive bacteria:

1. Respiratory infections: Lobar and bronchopneumonia, acute and chronic bronchitis, acute exacerbation of cystic fibrosis, bronchiectasis, empyema.
2. Ear, nose and throat infection: Otitis media, sinusitis, mastoiditis, especially infections due to Gram-negative bacteria.
3. Intra-abdominal and biliary tract infections: Infective diarrhoea, typhoid fever, cholangitis, cholecystitis.
4. Pelvic infections: Salpingitis, endometritis, pelvic inflammatory disease.
5. Urinary tract infections: Uncomplicated and complicated urethritis, cystitis, pyelonephritis, prostatitis, epididymitis.
6. Gonorrhoea- urethral, rectal and pharyngeal
7. Bone and joint infections: Osteomyelitis, septic.
8. Skin and soft tissue infections: Infected ulcers, wounds, abscesses, cellulitis, erysipelas, infected burns.
9. Systemic infections: Septicemia, peritonitis.

Dosage and Administration:
In adults, depending upon the type and severity of infection, C-Flox is given in a dose range of 250 mg-750 mg, administered twice daily for the period of 5-10 days.

Dosage and Administration in special situations:
In gonorrhoea, single dose of 250 mg (C-Flox-250) is given. In elderly patients no dosage adjustment is usually required. In patients with severe renal impairment (serum creatinine <20ml/minute), the usual dose may be reduced to half.

Contraindications, Warnings, Precautions:
A history of hypersensitivity to any of the quinolones is a contraindication to the use of C-Flox. C-Flox may cause CNS stimulation which may lead to tremor, restlessness or even seizures. So C-Flox should be used with caution in patients of epilepsy. Anaphylactic reactions have also been reported to the first dose of C-Flox.

The dose of C-Flox should be approximately adjusted in patients with impaired renal function. When prolonged therapy is given, the renal, hepatic and hemopoietic function must be periodically assessed.

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 C-Flox. Symptoms may occur soon after initiation of C-Flox and may be irreversible. C-Flox should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense and vibratory sensation.

<u>Cardiac disorder:</u>
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrome.
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia).
- Elderly.
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

<u>Disabling and potentially irreversible serious adverse reactions</u>
Fluoroquinolones, including C-Flox, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue C-Flox immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including C-Flox, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

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Aortic aneurysm or 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 a 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 dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally
- 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.

Psychiatric Adverse Reactions

Fluoroquinolones, including C-Flox, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving C-Flox, discontinue C-Flox immediately and institute appropriate measures.

Blood Glucose Disturbances

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with C-Flox. In C-Floxtreated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (for example, sulfonylurea) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue C-Flox and initiate appropriate therapy immediately.

Use in pregnancy, lactation & children:

It is not used in pregnancy. It is excreted into breast milk, so should not be given to nursing mothers. Safety and effectiveness of C-Flox has not been established in children.

Interactions with other drugs:

Concurrent administration of C-Flox with theophylline may lead to elevated plasma concentrations of theophylline. Ciprofloxacin also interferes with the metabolism of caffeine resulting in the prolongation of its plasma half-life. Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in lower plasma levels. Concurrent administration of ciprofloxacin and NSAIDs has been reported to increase the risk of CNS stimulation and seizures. Probenecid interferes with renal tubular secretion of ciprofloxacin and increases its serum concentrations.

Drugs known to prolong QT interval:

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

Side Effects:

C-Flox is generally well tolerated. The most frequently reported adverse reactions are nausea, diarrhoea, vomiting, abdominal pain/discomfort, headache, restlessness and rash. The additional side effects consist of insomnia, urticaria, and photosensitive reactions. Isolated cases of tendon inflammation have been reported which may lead to tendon rupture. Treatment should be discontinued immediately if these symptoms occur.

Cardiac Disorders:

Not known: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged.

Nervous system disorders (frequency not known):

Peripheral neuropathy (that may be irreversible) and polyneuropathy.

Overdosage:

Information on overdosage with C-Flox is not available. In the event of acute overdosage, stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment in the form of adequate hydration. Only a small amount (<10%) is removed from the body after haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Presentation:

Ciprofloxacin Tablets are packed in boxes of 10 blisters x 10 tablets.

Revised on 07 November 2020

Manufactured by:

INTAS

For 500mg:

INTAS PHARMACEUTICALS LTD.

Plot No. 457 & 458, Village-Matoda, Bavla Road, And
Plot No: 191/218 P, Village: Chacharwadi, Tal-Sanand,
Vill: Matoda & Chacharwadi-382210, Ahmedabad, Gujarat, India

INTAS PHARMACEUTICALS LTD.

Camp road, Selaqui, Dehradun, Uttarakhand, IN 248197, India

For 250mg:

INTAS PHARMACEUTICALS LTD.

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Plot No: 191/218 P, Village: Chacharwadi, Tal-Sanand,
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