1.6.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

1. Name of the Medicinal Product

CIPROQUIN-500 (Ciprofloxacin Tablets USP 500mg)

1.1 Strength

500 mg

1.2 Pharmaceutical Form

Tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration:

Each film coated tablet contains:

Ciprofloxacin Hydrochloride USP ……500 mg

2.2 Quantitative declaration:

Composition of unit dose is given below:

Ingredients	Reference	Pharmaceutical Function	Quantity/ Tab (mg)	% w/w
Ciprofloxacin Hydrochloride	USP	Active	582.00	91.37
Maize Starch	BP	Disintegrant/ Diluents	20.00	3.14
Sodium Starch Glycollate	BP/EP	Disintegrant	16.00	2.50
Purified water**	BP	Process Solvent	Q.S	--
Magnesium Stearate	BP	Lubricants	11.00	1.73
Colloidal Anhydrous silica	BP	Glidant	1.00	0.16
Instacoat White [IC-U-1308]	HS	Film former	7.00	1.10
		Total	637	100%

** - process solvent does not contribute to weight of tablet

BP - British Pharmacopoeia

EP- European Pharmacopoeia

HS - In-house Specification

USP- United State Pharmacopoeia

Q.S- Quantity sufficient

Molecular weight of Ciprofloxacin Hydrochloride = 385.8
Molecular weight of Ciprofloxacin = 331.34

$$\text{Conversion factor for Ciprofloxacin Hydrochloride} = \frac{385.8}{331.34} = 1.1641$$

500mg Ciprofloxacin = 1.1641 x 500 mg Ciprofloxacin Hydrochloride
500mg Ciprofloxacin = 582 mg Ciprofloxacin Hydrochloride

Qualitaitive Compostion of Instacoat White [IC-U-1308]:

Hydroxy Propyl methyl cellulose USP, Polyethylene Glycol USP/NF, Talc USP, Titanium dioxide USP.

2.3 Salts and hydrates

Ciprofloxacin Hydrochloride

2.4 Esters and pro-drugs

Not applicable

2.5 Oral Powders for solution or suspension

Not applicable

2.6 Parenterals excluding powders for reconstitution

Not applicable

2.7 Powders for reconstitution prior to parenteral administration

Not applicable

2.8 Concentrates

Not applicable

2.9 Transdermal patches

Not applicable

2.10 Multidose solid or semi-solid products

Not applicable

2.11 Biological medicinal products

Not applicable

3. Pharmaceutical form

Description: White colored, capsule shaped tablets, plain on one side & breakline on other side without any visible defect.

4 Clinical Particulars

4.1 Therapeutic indications

For the treatment of infections caused by susceptible strains of the designated micro-organisms in the conditions listed below:

Lower respiratory infections, Skin & skin structure infections, Bone and joint infections, Urinary tract infections and infections diarrhea caused by E.Coli (enterotoxigenic strains), Campylobacter jejuni, Shigella Flexneri and Shigella sonnel when antibacterial therapy is indicated.

4.2 Posology and Method of Administration

Posology

Urinary tract infections: 250mg. every 12 hours. Complicated infections caused by organisms not highly susceptible : 500mg. every 12 hours.

Respiratory tract infections, skin and skin structure infections and bone and joint infections ; 500mg, every 12 hours. More severe or complicated infections:750mg. every 12 hours.

Infectious diarrhea: 500 mg. every 12 hours.

The duration of treatment depends upon the severity of infection. Generally, continue ciprofloxacin for atleast 2 days after the signs and symptoms of infection have disappeared.

The usual duration is 7 to 14 days; however, for severe and complicated infections, more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 week or longer. Infectious diarrhoea may be treated for 5 to 7 days.

The need for liberal water intake during Ciprofloxacin therapy should be impressed upon the patients.

4.3 Method of Administration

Administration via Oral route. To be taken with a glass of water.

4.4 Contraindications

Hypersensitivity to Ciprofloxacin or any other Quinolones is a contraindication to its use. Children below 12 years should not be put on Ciprofloxacin Therapy.

4.5 Special warnings and precautions for use

Precautions

CNS stimulation may occur with ciprofloxacin, as with other quinolones, which may lead to tremor, restlessness, lightheadedness, confusion and very rarely to hallucinations or convulsive seizures. Use with caution in patients with known or suspected CNS disorders, such as severe celebral arteriosclerosis or epilepsy, or other factors which predispose to seizures. Crystalluria related to ciprofloxacin has been reported only rarely in man because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated and should avoid alkalinity of the urine. Do not exceed the recommended daily dose.

Superinfection : Use of antibiotics (especially prolonged or repeated therapy) may result in bacterial or fungal overgrowth of nonsusceptible organisms. Such overgrowth may lead to a secondary infection. Take appropriate measures if superinfection occurs.

Warnings

Tendinitis: At any sign of tendinitis (e.g.painful swelling) the administration of Ciprofloxacin should be discontinued, physical exercises be avoided, and a physician consulted.

4.6 Pediatric population

Ciprofloxacin Hydrochloride is a Fluoroquinolone antibiotic widely used in adults due to their broad spectrum of activity. However, because preclinical animal studies suggested cartilage toxicity, use of these agents has not been encouraged in children.

4.7 Interactions with other medicinal products and other forms of interactions

Caution if concomitant use with other drugs known to prolong the QT interval.

4.8 Pregnancy and Lactation

Pregnancy

Ciprofloxacin should be avoided in pregnancy because it has been shown to cause arthropathy in animal studies; safer alternatives are available; however, a single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.

Breast-feeding

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.9 Effects on ability to drive and use machine

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

4.10 Undesirable effects

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

Infections and infestations	
Rare	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)
Blood and lymphatic system disorders	
Rare	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia
Psychiatric disorders	
Rare	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations
Uncommon	Psychomotor hyperactivity / agitation

Nervous system disorders	
Rare	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures ,Vertigo
Eye disorders	
Rare	Visual disturbances (e.g. diplopia)
Cardiac disorders	
Rare	Tachycardia
Frequency not known	Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular disorders	
Rare	Vasodilatation Hypotension Syncope
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	
Common	Nausea Diarrhoea
Uncommon	Vomiting Gastro-intestinal and abdominal pains Dyspepsia Flatulence

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

4.11 Overdose and antidote

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

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

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

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

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

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 and recombination.

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.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, 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 400mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution:

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism:

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 Pre-clinical 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.

Mutagenicity: Ciprofloxacin is non-mutagenic in Ames bacteria test, unscheduled *in vivo* DNA synthesis, *in-vivo* micronucleus mouse test and *in-vitro* chromosome aberration CHO cells.

Carcinogenicity: Ciprofloxacin is non-carcinogenic

Teratogenicity: Ciprofloxacin is found to be non-teratogenic in Ames bacteria test, unscheduled *in vivo* DNA synthesis, *in-vivo* micronucleus mouse test and *in-vitro* chromosome aberration CHO cells.

6 Pharmaceutical Particulars

6.1 List of Excipients-

Ingredients	Reference
Maize Starch	BP
Sodium Starch Glycollate	EP/BP
Purified water	BP
Magnesium Stearate	BP
Colloidal Anhydrous silica	BP
Instacoat White [IC-U-1308]	HS

6.2 Incompatibilities:

None

6.3 Shelf life:

Proposed shelf life: 36 Months (3 years)

6.4 Special precautions for storage:

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

Alu/ PVC blister of 10x10

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder.

KOPRAN LIMITED
Village Savroli, Taluka Khalapur,
District-Raigad-410202
India

8. Marketing authorization registration number(s).

Applied for registration

9. Date of first authorization registration/renewal of the authorization:

Not applicable

10. Date of revision (if any) of this text.

Not applicable

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IFAPPLICABLE)

Not applicable