1.3 Product Information
1.3.1 Summary of product characteristics (SmPC)
1. 3.1.1 Name of the medicinal product:
CIPROGUD (Ciprofloxacin Tablets USP 500 mg)

1.3.1.2 Qualitative and quantitative composition:

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
a)	**Dry Mixing**					
1.	Ciprofloxacin hydrochloride	USP	Ciprofloxacin Hydrochloride USP equivalent to Ciprofloxacin 500 mg	NA	582.000	Active
2.	Maize starch	BP	NA	NA	43.000	Diluent
b)	**Binder Preparation**					
3.	Maize starch	BP	NA	NA	25.000	Binder
4.	Purified water	BP	NA	NA	-----	Vehicle
c)	**Lubrication**					
5.	Sodium starch glycolate	BP	NA	NA	28.000	Disintegrant
6.	Purified talc	BP	NA	NA	4.000	Glidant
7.	Magnesium stearate	BP	NA	NA	10.000	Lubricant
8.	Croscarmellose sodium	BP	NA	NA	8.000	Disintegrant
9.	Colloidal anhydrous silica	BP	NA	NA	10.000	Lubricant
10.	Succinic acid	BP	NA	NA	40.000	pH modifier
	Average weight of uncoated tablet (In mg)				**750.000**	
d)	**Film Coating**					
11.	Hypromellose (15 CPS)	BP	NA	NA	14.200	Film Former
12.	Purified talc	BP	NA	NA	2.860	Antiadherant
13.	Macrogol-6000	BP	NA	NA	1.050	Plasticizer
14.	Titanium dioxide	BP	NA	NA	1.890	Colour
15.	Isopropyl alcohol	BP	NA	NA	--	Solvent
16.	Dichloromethane	BP	NA	NA	--	Solvent
	Average weight of film coated tablet (In mg)				**760.00**	

1.3.1.3 Pharmaceutical form: Film coated tablets

Description: White coloured, capsule shaped, biconvex, film coated tablet having breakline on one side and plain on other side.

1.3.1.4 Clinical Particulars
1.3.1.4.1 Therapeutic indications
CIPROGUD (Ciprofloxacin Tablets USP 500mg) are indicated for the treatment of the following infections-

Adults

• Lower Respiratory tract infections due to Gram-negative bacteria
- Pneumonia
- Exacerbations of chronic obstructive pulmonary disease
- 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-negative bacteria
• Urinary tract infections
• Genital tract infections
- Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
- Epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*

• Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
• Intra-abdominal infections
• Infections of the skin and soft tissue caused by Gram-negative bacteria
• Malignant external otitis
• Infections of the bones and joints
• Prophylaxis of invasive infections due to *Neisseria meningitidis*
• 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.

Children and adolescents

• Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
• Complicated urinary tract infections and 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.

1.3.1.4.2 Posology and method of administration
Route: Oral
Method of Administration:
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

Indications	Daily dose in mg	Total duration of treatment (potentially including initial

			parenteral treatment with ciprofloxacin)
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	At least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	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 twice daily	At least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	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	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days

Bone and joint infections	500 mg twice daily to 750 mg twice daily	Max. of 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.	500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*	500 mg as a single dose	1 day (single dose)
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.	500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Paediatric population

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with Ciprofloxacin)**
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	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.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	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 m^2]**	**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

1.3.1.4.3 Contraindications

Hypersensitivity to the active substance or other Quinolones or to any of the excipients used. Concomitant administration of Probenecid, Metoclopramide, Omeprazole, Agomelatine, Zolpidem, Methotrexate, Theophylline, Phenytoin, Tizanidine etc

1.3.1.4.4 Special warnings and precautions for use

Streptococcal Infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

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 must be co-administered with other appropriate antibacterial agents.

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 should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless Ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded based on local prevalence data. 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 fluoroquinolones.

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 treatment duration. This is all the more to be taken into account as regards to the increasing resistance level 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' diarrhoea

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 data together 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 experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents. Treatment should be initiated only after a careful benefit/ risk evalulation, due to possible adverse events related to joints and/ or surrounding tissue.
Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised 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 significant between
groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to 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.
Clinical trials have included children and adolescents aged 1-17 years.
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 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 tendon disease/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 (especially Achilles tendon), sometimes bilateral, may occur with Ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of Ciprofloxacin therapy. The risk of

tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids at any sign of tendinitis (e.g. painful swelling, inflammation), Ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis.

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 occur Ciprofloxacin should be discontinued. Psychiatric reactions may occur even after first administration of Ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, Ciprofloxacin should be discontinued.

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an 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 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)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including Ciprofloxacin, in these populations.

Hypoglycemia

As with other quinolones, hypoglycemia has been reported most often in diabetic patients, predominantly in the elderly population. In all 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 super infection. 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. Therefore, patients taking these substances concomitantly with Ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary.
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.
Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:
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).
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:

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) when given concomitantly with Ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

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 in a 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.

Zolpidem

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

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 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 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 a clinical 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 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

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.

1.3.1.4.6 Pregnancy and Lactation

Pregnancy

The data that are available on administration of Ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of Ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus.
As a precautionary measure, it is preferable to avoid the use of Ciprofloxacin during pregnancy.

Lactation

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

1.3.1.4.7 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.

1.3.1.4.8 Undesirable effects

All medicines may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most common side effects persist or become bothersome:
Diarrhea; dizziness; headache; nausea; vomiting
Seek medical attention right away if any of these severe side effects occur:

Severe allergic reactions (rash; hives; itching; difficulty breathing or swallowing; tightness in the chest or throat; swelling of the mouth, face, lips, or tongue); bloody or tarry stools; chest pain; fainting; fast or irregular heartbeat; fever, chills, or unusual cough; hallucinations; inability to move or bear weight on a joint or tendon area; mood or mental changes (eg, new or worsening anxiety, agitation, confusion, depression, nervousness, nightmares, paranoia, restlessness,
sleeplessness); muscle pain or weakness; pain, soreness, redness, swelling, weakness, or bruising of a tendon or joint area; persistent sore throat; seizures; severe or persistent dizziness or headache; shortness of breath or trouble breathing; suicidal thoughts or actions; sunburn; symptoms of kidney problems (eg, not able to pass urine, change in how much urine is passed, blood in the urine, a big weight gain); tremors; unusual bruising or bleeding; unusual tiredness or weakness; vaginal yeast infection; vision changes.

1.3.1.4.9 Overdose

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

1.3.1.5 Pharmacological properties

1.3.1.5.1 Pharmacodynamic properties

Ciprofloxacin is a broad-spectrum anti-infective agent of the fluoroquinolone class. Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian.
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, strand supercoiling repair, and recombination.

1.3.1.5.2 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 (C_{max}) 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 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.

Biotransformation

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). 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.

Excretion of Ciprofloxacin (% of dose)

	Oral administration	
	Urine	Faeces
Ciprofloxacin Metabolites (M1- M4)	44.7 11.3	25.0 7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of Ciprofloxacin of up to 12 h.

Non-renal clearance of Ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

1.3.1.5.3 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.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1 List of excipients

Maize starch, Purified talc, Magnesium stearate, Colloidal anhydrous silica, Croscarmellose sodium, Hypromellose (15 CPS), Titanium dioxide, Macrogol-6000, Sodium starch glycolate, Succinic acid, Isopropyl alcohol and Dichloromethane

1.3.1.6.2 Incompatibilities

Not applicable

1.3.1.6.3 Shelf life

36 months

1.3.1.6.4 Special precautions for storage

Store in a cool, dry & dark place.
Keep all medicines out of reach of children

1.3.1.6.5 Nature and contents of container

Primary packing: 10 Tablets in an ALU-ALU blister.
Secondary packing: 1 Blister is packed in an inner carton along with leaflet.
Tertiary packing: 10 Inner cartons are packed in an outer carton. Shrink individual outer carton. Such 40 Shrinks are packed in a 5 Ply shipper sealed with BOPP tape & strap with strapping roll.

1.3.1.6.6 Special precautions for disposal and other handling

None

1.3.1.7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. IBU PHARMA NIG. LTD.** No.:1, Labiran Street, Ikenne Ogun State, Nigeria
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
Contact person's phone number	+91 7350864803
Contact person's email	pravin.patil@kamlagroup.co.in