1. Name of the medicinal product

Emzor Ciprofloxacin 500mg Film-Coated Tablets

2. Qualitative and quantitative composition

Each Emzor Ciprofloxacin 500mg Tablet contains 582.20 mg Emzor Ciprofloxacin hydrochloride equivalent to 500mg Emzor Ciprofloxacin (INN).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated Tablets.

Emzor Ciprofloxacin 500mg tablets are white to off-white, capsule shape, biconvex with beveled edge, film coated tablet with inscription 'CI' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Emzor Ciprofloxacin are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to Emzor Ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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)

Emzor 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)

Emzor 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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to Emzor 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 Emzor 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 Emzor 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 (see section 4.4)	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		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Emzor Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.			
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.		500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure
Drug administration should begin as soon as possible after suspected or confirmed exposure.			

Paediatric population

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with Emzor 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 m²]	**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

In patients with impaired liver function, no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Emzor Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit -juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous Emzor Ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

Concomitant administration of Emzor Ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Streptococcal Infections (including Streptococcus pneumoniae)

Emzor 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

Emzor 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 Emzor 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, Emzor Ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if Emzor Ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical Emzor Ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless Emzor 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 Emzor 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 the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

There are limited data on the efficacy of Emzor Ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea

The choice of Emzor Ciprofloxacin should take into account information on resistance to Emzor Ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints

Emzor 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 Emzor Ciprofloxacin in children and adolescents should follow available official guidance. Emzor 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 (see section 4.8).

Emzor Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on Emzor Ciprofloxacin use in children (Emzor 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 (see section 4.8).

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

Emzor 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 a Emzor Ciprofloxacin use.

The use of Emzor 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 (see section 4.8) and may be life-threatening. If such reaction occurs, Emzor Ciprofloxacin should be discontinued and an adequate medical treatment is required.

Musculoskeletal System

Emzor 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, Emzor 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 Emzor Ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with Emzor Ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of Emzor Ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8). At any sign of tendinitis (e.g. painful swelling, inflammation), Emzor Ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.

Emzor Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity

Emzor Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking Emzor Ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System

Emzor Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Emzor Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur Emzor Ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after first administration of Emzor 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, Emzor 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 Emzor Ciprofloxacin. Emzor 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 (see section 4.8).

Cardiac disorders

Caution should be taken when using fluoroquinolones, including Emzor 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 Emzor Ciprofloxacin, in these populations.

(See section 4.2 Geriatric patients, section 4.5, section 4.8, section 4.9). 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 (see section 4.8).

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 (see section 4.8). In such cases, Emzor 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 Emzor Ciprofloxacin has been reported (see section 4.8). Patients receiving Emzor Ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since Emzor Ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of Emzor Ciprofloxacin.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with Emzor Ciprofloxacin (see section 4.8). 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 Emzor Ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Emzor 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 Emzor Ciprofloxacin bacteria that demonstrate resistance to Emzor Ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for Emzor Ciprofloxacin- resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused
by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450

Emzor 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 Emzor Ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with Emzor Ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

The concomitant use of Emzor Ciprofloxacin with methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in-vitro* activity of Emzor Ciprofloxacin against *Mycobacterium tuberculosis* might give falsenegative bacteriological test results in specimens from patients currently taking Emzor Ciprofloxacin.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Effects of other products on Emzor Ciprofloxacin:

Drugs known to prolong QT interval

Emzor 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) (see section 4.4).

Chelation complex formation

The simultaneous administration of Emzor 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 Emzor Ciprofloxacin. Consequently, Emzor 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 Emzor Ciprofloxacin should be avoided because absorption of Emzor Ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of Emzor Ciprofloxacin. Co-administration of probenecid and Emzor Ciprofloxacin increases Emzor Ciprofloxacin serum concentrations.

Metoclopramide

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

Omeprazole

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

Effects of Emzor Ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with Emzor Ciprofloxacin (see section 4.3). 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 Emzor 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 Emzor Ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration ('Cytochrome P450' in section 'Special warnings and precautions for use).

Zolpidem

Co-administration Emzor 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 Emzor Ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of Emzor 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 (see section 4.4).

Other xanthine derivatives

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

Phenytoin

Simultaneous administration of Emzor 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 Emzor 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 Emzor 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 Emzor 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 Emzor 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 Emzor Ciprofloxacin, similar effects can be expected upon concomitant administration (see section 4.4).

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with Emzor 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 Emzor Ciprofloxacin (see section 4.4).

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with Emzor 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 Emzor Ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Emzor 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 Emzor Ciprofloxacin are advised (see section 4.4).

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 Emzor Ciprofloxacin. Therefore, caution should be used prescribing Emzor Ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

4.6 Fertility, pregnancy and lactation

Pregnancy

The data that are available on administration of Emzor Ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of Emzor 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 (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Emzor Ciprofloxacin during pregnancy.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with Emzor Ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of Emzor Ciprofloxacin.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1 000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1 000	**Very Rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis	Haemolytic anaemia Agranulocytosis	

			Thrombocytopenia Thrombocytaemia	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia, Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section 4.4).
Psychiatric Disorders		Psychomotor hyperactivity / agitation	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	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	Mania, hypomania
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension Pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye Disorders			Visual disturbances (e.g. diplopia)	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk

					factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastro-intestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP) DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome
Musculo- skeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4)		

			Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)
Endocrine Disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard

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 Emzor Ciprofloxacin in overdoses

Only a small quantity of Emzor 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. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone Antibacterials, fluoroquinolones ,ATC code: J 01 MA 02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of Emzor Ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of Emzor 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 Emzor 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 Emzor 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 Emzor Ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteriaceae	S ≤0.5 mg/L	R > 1 mg/L
Pseudomonas spp	S ≤0.5 mg/L	R > 1 mg/L
Acinetobacter spp	S ≤1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤1 mg/L	R > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	S ≤0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤0.5 mg/L	R > 1 mg/L
1 *Staphylococcus* spp. - breakpoints for Emzor Ciprofloxacin relate to high dose therapy. * Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.		

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to Emzor Ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis*

Haemophilus ducreyi *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms *Mobiluncus*
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*+ *Burkholderia cepacia*+ * *Campylobacter* spp.+ * *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms

Mycoplasma genitalium *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral Emzor Ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Protein binding of Emzor Ciprofloxacin is low (20-30%). Emzor 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. Emzor 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: desethyleneEmzor Ciprofloxacin (M 1), sulphoEmzor Ciprofloxacin (M 2), oxoEmzor Ciprofloxacin (M 3) and formylEmzor Ciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Emzor Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Emzor 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 Emzor Ciprofloxacin (% of dose)

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

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

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

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

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, Emzor Ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of Emzor 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, Emzor 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, Emzor Ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. Pharmaceutical particulars

6.1 List of excipients

Each tablet contains:

- croscarmellose sodium,

- microcrystalline cellulose,

- povidone,

- magnesium stearate.

The tablet film-coat consists of:

- hypromellose,

- lactose monohydrate,

- titanium dioxide E171,

- macrogol 4000,

- sodium citrate

- purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life
5 years

6.4 Special precautions for storage
Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container
PVC 250 µm//Al 20 µm blisters.

The Emzor Ciprofloxacin 500mg Tablets are available in pack sizes of 10, 12, 20 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special instructions for use/handling.

7. Marketing authorisation holder

Emzor Pharmaceutical Industries Limited

Km 1 Flowergate Mixed Development Scheme, Sagamu/Benin Expressway,Makun,Sagamu,Ogun-State.

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorisation

NA

10. Date of revision of the text

NA