

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 36 of 81

## 1.5 Product Information

### 1.5.1 Summary of Product Characteristics (SPC)

#### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1. NAME OF THE MEDICINAL PRODUCT

Fluoxetine<sup>®</sup> 500 film-coated tablets

Fluoxetine<sup>®</sup> 750 film-coated tablets

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluoxetine 500: Fluoxetine film-coated tablets contain 500 mg of ciprofloxacin (as ciprofloxacin hydrochloride) per tablet.

Fluoxetine 750: Fluoxetine film-coated tablets contain 750 mg of ciprofloxacin (as ciprofloxacin hydrochloride) per tablet.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Scored, film-coated tablets

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Special attention should be paid to available information on resistance to 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
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Gonococcal urethritis and cervicitis

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 37 of 81

- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*.
  - Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*
- In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

- 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
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

#### 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 (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 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

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 38 of 81

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 urethritis and cervicitis	500 mg as a single dose

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 39 of 81

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intraabdominal infections	Diarrhoea caused by bacterial pathogens including <i>Shigella</i> spp. other than <i>Shigella dysenteriae</i> type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily
	Diarrhoea caused by <i>Shigella dysenteriae</i> type 1	500 mg twice daily
	Diarrhoea caused by <i>Vibrio cholerae</i>	500 mg twice daily
	Typhoid fever	500 mg twice daily
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily
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

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 40 of 81

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Treatment of infections or prophylaxis of infections in neutropenic patients 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 <i>Neisseria meningitidis</i>	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 <i>Bacillus anthracis</i> exposure

#### Children and adolescents

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 <i>Bacillus anthracis</i> exposure

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 41 of 81

Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections
-------------------------	---	-------------------------------------

#### Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

#### Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m <sup>2</sup> ]	Serum Creatinine [ $\mu$ mol/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. 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 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 ciprofloxacin and tizanidine (see section 4.5).

#### 4.4 Special warnings and precautions for use

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.

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 42 of 81

Streptococcal Infections (including *Streptococcus pneumoniae*)

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

Genital tract infections

Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

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.

Children and adolescents

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.

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.

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 43 of 81

#### 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 a 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 (see section 4.8) 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, as soon as the first 48 hours of treatment. 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), 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 (see section 4.8).

#### 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 (see section 4.8).

#### Central Nervous System

Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders, which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or



EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 44 of 81

psychosis can progress to self-endangering behaviour. In these 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 (see section 4.8).

#### Cardiac disorders

Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

#### 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, 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 (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

#### Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with 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 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 superinfection. 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, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 45 of 81

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 (see section 4.5).

#### Methotrexate

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

#### 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

#### Effects of other products on ciprofloxacin:

##### 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), 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 H<sub>2</sub> 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.

#### Effects of ciprofloxacin on other medicinal products:

##### Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration ( $C_{max}$  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.

##### Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 46 of 81

risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

#### 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 (see section 4.4).

#### 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.

#### Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

#### 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  $C_{max}$  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 (see section 4.4).

#### 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 coadministration with ciprofloxacin are advised (see section 4.4).

## 4.6 Fertility, 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

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 47 of 81

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 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.

#### 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.

#### 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 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 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	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		

EXPHAR SA	May 2019		FLUOXINE 500 – Tablets	
	Administrative Information and Product Information		Module 1 - Page 48 of 81	

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)
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytæmia	Haemolytic anaemia Agranulocytosis Pancytopenia (lifethreatening) Bone marrow depression (lifethreatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (lifethreatening) (see section 4.4) Serum sickness like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 49 of 81

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)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait Disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral Neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour Distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes*
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	

EXPHAR SA	May 2019		FLUOXINE 500 – Tablets	
	Administrative Information and Product Information		Module 1 - Page 50 of 81	

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)
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal 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)	

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 51 of 81

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)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially lifethreatening) ) Toxic epidermal necrolysis (potentially lifethreatening) )	
Musculoskeletal, 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)	



EXPHAR SA	May 2019		FLUOXINE 500 – Tablets	
	Administrative Information and Product Information		Module 1 - Page 52 of 81	

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)
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	Prothrombin level abnormal Increased amylase		Increased INR (International Normalized Ratio) (in patients treated with vitamin K antagonists)

\* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

#### 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).

#### 4.9 Overdose

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 53 of 81

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, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.

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

## 5. 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.

#### PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum ( $C_{max}$ ) 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.

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

#### Spectrum of antibacterial activity:

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 54 of 81

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

#### EUCAST Recommendations

Microorganisms	Susceptible	Resistant
<i>Enterobacteria</i>	S ≤ 0.5 mg/L	R > 1 mg/L
<i>Pseudomonas</i>	S ≤ 0.5 mg/L	R > 1 mg/L
<i>Acinetobacter</i>	S ≤ 1 mg/L	R > 1 mg/L
<i>Staphylococcus</i> spp. <sup>1</sup>	S ≤ 1 mg/L	R > 1 mg/L
<i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i>	S ≤ 0.5 mg/L	R > 0.5 mg/L
<i>Neisseria gonorrhoeae</i>	S ≤ 0.03 mg/L	R > 0.06 mg/L
<i>Neisseria meningitidis</i>	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L

<sup>1</sup> *Staphylococcus* spp. - breakpoints for 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 ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

<b>COMMONLY SUSCEPTIBLE SPECIES</b>
<u><i>Aerobic Gram-positive micro-organisms</i></u> <b><i>Bacillus anthracis</i> (1)</b>
<u><i>Aerobic Gram-negative micro-organisms</i></u> <i>Aeromonas</i> spp. <i>Brucella</i> spp. <i>Citrobacter koseri</i> <i>Francisella tularensis</i> <i>Haemophilus ducreyi</i> <i>Haemophilus influenzae</i> * <i>Legionella</i> spp. <i>Moraxella catarrhalis</i> * <i>Neisseria meningitidis</i>

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 55 of 81

*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*<sup>+</sup>  
*Burkholderia cepacia*<sup>+</sup>\*  
*Campylobacter* spp.<sup>+</sup>\*  
*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*  
*Enterococcus faecium*

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 56 of 81

<i>Listeria monocytogenes</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Stenotrophomonas maltophilia</i>
<u>Anaerobic micro-organisms</u> <i>Excepted as listed above</i>
<u>Other micro-organisms</u> <i>Mycoplasma genitalium</i> <i>Ureaplasma urealitycum</i>
<p>* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications</p> <p>+ Resistance rate <math>\geq 50\%</math> in one or more EU countries</p> <p>(\$): Natural intermediate susceptibility in the absence of acquired mechanism of resistance</p> <p>(1): Studies have been conducted in experimental animal infections due to inhalations of <i>Bacillus anthracis</i> 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 <i>in-vitro</i> susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral 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.</p> <p>(2): Methicillin-resistant <i>S. aureus</i> 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.</p>

## 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 nonionised 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

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 57 of 81

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 (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	44.7	25.0
Metabolites (M <sub>1</sub> -M <sub>4</sub> )	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. 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.

#### 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

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 58 of 81

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.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

FLUOXINE 500: Maize starch, microcrystalline cellulose, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), talc, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate, sodium croscarmellose (sodium carboxymethylcellulose), hydroxypropylmethylcellulose, titanium dioxide (E171); polyethyleneglycol 6000, tartrazine lake (E102).

FLUOXINE 750: Maize starch, microcrystalline cellulose, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), talc, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate, sodium croscarmellose (sodium carboxymethylcellulose), hydroxypropylmethylcellulose, titanium dioxide (E171); polyethyleneglycol 6000.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Keep in the original packaging, protected from heat, light and humidity. Store below 30 °C.

**6.5 Nature and contents of container**

EXPHAR SA	May 2019	FLUOXINE 500 – Tablets
	Administrative Information and Product Information	Module 1 - Page 59 of 81

Box of 10 tablets in PVC/aluminium blister

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Exphar s.a.  
Zoning Industriel Nivelles Sud, Zone II,  
Avenue Thomas Edison 105  
1402 Thines - Belgium  
Tel +32.(0)67 68 84 05  
Fax +32.(0)67 68 84 19

### **8. MANUFACTURER**

Gracure Pharmaceuticals Ltd.,  
E-1105, Industrial Area, Phase-III,  
Bhiwadi, Dist. Alwar (Raj.) - India  
Tel +91.11.259.207.48  
Fax +91.11.259.207.47

### **9. DATE OF REVISION OF THE TEXT**

January 2018