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

CEFIPOWER
(Cefixime and Ofloxacin Tablets)

COMPOSITION
Each film coated tablet contains:
Cefixime I.P. equivalent to Cefixime Anhydrous…..200 mg
Ofloxacin I.P. ……200 mg
Excipients……...q.s.
Colour: Tartrazine

INDICATIONS
For the treatment of patients with typhoid fever and urinary tract infection in adults.

DOSAGE AND ADMINISTRATION
Ofloxacin
Posology

The dose of ofloxacin is determined by the type and severity of the infection. The dosage range for adults is 200 mg to 800 mg daily.

Up to 400 mg may be given as a single dose, preferably in the morning. Generally, individual doses should be given at approximately equal intervals.

In individual cases it may be necessary to increase the dose to a maximum total dose of 800 mg daily, which should be given as 400 mg twice daily, at approximately equal intervals. This may be appropriate in infections due to pathogens known to have reduced or variable susceptibility to ofloxacin, in severe and/or complicated infections (e.g. of the respiratory or urinary tracts) or if the patient does not respond adequately.

he following doses are recommended:

Indications	*Single and Daily Doses*
Uncomplicated urethral/ cervical gonorrhoea	400 mg
Uncomplicated lower urinary tract infections	200 mg-400 mg daily
Complicated infections of the upper urinary tract	400 mg daily, increasing if necessary, to 400 mg twice a day
Lower respiratory tract infections	400 mg daily, increasing, if necessary, to 400 mg twice a day
Non-gonococcal urethritis and cervicitis	400 mg daily

A single dose of 400 mg of ofloxacin is sufficient for the treatment of uncomplicated gonorrhoea.

Special patient populations

Impaired renal function

Following a normal initial dose, dosage should be reduced in patients with impairment of renal function as determined by creatinine clearance or plasma creatinine level.

Creatinine Clearance	*Plasma Creatinine*	*Maintenance Dose**
20 to 50 ml/min*	1.5 to 5 mg/dl	100 mg - 200 mg ofloxacin per day)
<20ml/min**	>5 mg/dl	100 mg ofloxacin per day

* According to indication or dose interval

** The serum concentration of ofloxacin should be monitored in patients with severe renal impairment and dialysis patients.

Patients undergoing haemodialysis or peritoneal dialysis should be given 100 mg ofloxacin per day.

When creatinine clearance cannot be measured, it can be estimated with reference to the serum creatinine level using the following Cockcroft's formula for adults:

$$\text{Men: } \text{ClCr (ml/min)} = \frac{\text{weight(kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dl)}}$$

or

$$\text{ClCr (ml/min)} = \frac{\text{weight(kg)} \times (140 - \text{age in years})}{0.814 \times \text{serum creatinine (µmol/l)}}$$

$$\text{Women: } \text{ClCr (ml/min)} = 0.85 \times (\text{above value})$$

Impaired liver function

The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction.

(e.g. cirrhosis of the liver with ascites). In such cases, it is recommended that the dose should not exceed 400 mg ofloxacin daily, because of possible reduction of excretion.

Paediatric population

Ofloxacin is contraindicated for use in children or growing adolescents.

Elderly

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal or hepatic function.

Duration

Treatment should not exceed 2 months duration.

A daily dose of up to 400 mg ofloxacin may be given as a single dose. In this case, it is preferable to administer ofloxacin in the morning.

Daily doses of more than 400 mg must be divided into two separate doses and be given at approximately equal intervals.

Method of administration

For oral use.

Ofloxacin tablets should be swallowed whole with sufficient liquid before or during meal times. They should not be taken within two hours of mineral antacids, sucralfate or metal ion preparations (aluminium, iron, magnesium or zinc), didanosine chewable or buffered tablets (for HIV), since reduction of absorption of ofloxacin can occur.

Cefixime
The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

Posology

Adults and Children over 10 Years or weighing more than 50 kg:
The recommended adult dosage is 200-400 mg daily according to the severity of infection, given either as a single dose or in two divided doses.

Elderly:
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment (See "Dosage in Renal Impairment").

Children under 10 Years:
Cefixime 200 mg are not recommended for use in children under 10 years old.

The safety and efficacy of cefixime has not been established in children less than 6 months.

Renal Impairment:
Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

Method for administration
For oral administration.

Absorption of cefixime is not significantly modified by the presence of food.

CONTRAINDICATIONS
Ofloxacin
The use of ofloxacin is contraindicated as follows:

• Hypersensitivity to the active substance, to any other fluoroquinolone antibacterials, or to any of the excipients.

• In patients with a history of epilepsy or an existing central nervous system disorder with a lowered seizure threshold.

• In patients with a history of tendon disorders related to fluoroquinolone administration

• In children or growing adolescents, and in pregnant or breastfeeding women, since animal experiments do not entirely exclude the risk of damage to the growth-plate cartilage in the growing organism cannot be entirely excluded.

• In patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity because they may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

Cefixime
Patients with known hypersensitivity to cephalosporin or Penicillin antibiotics

WARNINGS AND PRECAUTION
Ofloxacin
Ofloxacin tablets are not the drug of first choice in pneumonia caused by *Streptococcus pneumoniae* or *Chlamydia pneumoniae*.

Methicillin-resistant S. aureus

Are very likely to possess co-resistance to fluoroquinolones, including ofloxacin. Therefore ofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to ofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Resistance to fluoroquinolones of E. 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 E. coli to fluoroquinolones.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with ofloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Tendonitis

Tendonitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with ofloxacin and have been reported up to several months after discontinuation of ofloxacin. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years and in patients using corticosteroids. The daily dose should be adjusted in

elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed ofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with ofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Hypersensitivity

Hypersensitivity and allergic reactions have been reported for fluoroquinolones after first administration. Anaphylactic and anaphylactoid reactions can progress to life-threatening shock, even after the first administration. In these cases ofloxacin should be discontinued and suitable treatment (e.g. treatment for shock) should be initiated.

Diseases caused by Clostridium difficile

Diarrhoea, especially if severe, persistent and/or bloody, occurring during or after treatment with ofloxacin (including several weeks after treatment), may indicate a condition caused by *Clostridium difficile*, the most severe form of which is pseudomembranous colitis (CDAD) CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with ofloxacin. If pseudo-membraneous colitis is suspected, treatment should be discontinued immediately.

Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Medicinal products that inhibit peristalsis are contraindicated in such cases.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history epilepsy or with a known predisposition to seizures.

Patients with a known predisposition to seizures may include those with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs (NSAIDs), or with drugs which lower the cerebral seizure threshold, such as theophylline.

In case of convulsive seizures, treatment with ofloxacin should be discontinued.

Patients with impaired renal function

Since ofloxacin is eliminated primarily via the kidneys, the dose should be adjusted in patients with impaired renal function.

Patients with history of psychotic disorder

Psychotic reactions have been reported in patients receiving fluoroquinolones including ofloxacin. In some cases these have progressed to suicidal thoughts or self-endangering behavior including suicide attempt, sometimes after a single dose of ofloxacin. In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted.

Ofloxacin should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

Patients with impaired liver function

Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Patients treated with vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Myasthenia gravis

Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Ofloxacin is not recommended in patients with a known history of myasthenia gravis.

Superinfection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms, especially Enteracci, resistant strains of some organisms or Candida. Repeated evaluation of the patient's condition is essential and periodic *in vitro* susceptibility tests may be useful. If secondary infection occurs during therapy, appropriate measures should be taken.

Prevention of photosensitisation

Photosensitisation has been reported with ofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

QT interval prolongation

Very rare cases of QT interval proplongation have been reported in patients taking fluoroquinolones.

Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

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

- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia) - 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)

- - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, 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 these diabetic patients, careful monitoring of blood glucose is recommended.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including ofloxacin, which can be rapid in its onset. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition.

Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate-dehydrogenase deficiency may be predisposed to haemolytic reactions if they are treated with quinolones. Therefore if ofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Interference with laboratory tests

In patients treated with ofloxacin, determination of opiates or porphyrin levels in urine may give false-positive results. It may be necessary to confirm positive opiate or porphyrin screens by more specific methods.

Vision disorders

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

Cefixime
Encephalopathy

Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs.

Hypersensitivity to penicillins

As with other cephalosporins, cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with cefixime, the drug should be discontinued and the patient treated with appropriate agents if necessary.

Haemolytic anaemia

Drug-induced haemolytic anaemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia has also been reported.

Acute renal failure

As with other cephalosporins, cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Renal impairment

Cefixime should be administered with caution in patients with markedly impaired renal function.

Paediatric use

Safety of cefixime in premature or newborn infant has not been established.

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment.

Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

DRUG INTERACTIONS

Ofloxacin

Antacids, Sucralfate, Metal Cations

Co-administered magnesium/aluminum antacids, sucralfate, zinc or iron preparations and didanosine chewable/buffered tablets can reduce absorption of ofloxacin tablets. Therefore, ofloxacin should be taken 2 hours before such preparations.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of ofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, nonsteroidal antiinflammatory drugs, or other agents, which lower the seizure threshold.

Probenecid, cimetidine, furosemide, and methotrexate

Probenecid decreased the total clearance of ofloxacin by 24%, and increased AUC by 16%. The proposed mechanism is a competition or inhibition for active transport at the renal tubular excretion. Caution should be exercised when ofloxacin is coadministered with drugs that affect the tubular renal secretion such as probenecid, cimetidine, furosemide and methotrexate.

Drugs known to prolong QT interval

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

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with ofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should, therefore, be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

Glibenclamide

Ofloxacin may cause a slight increase in plasma glibenclamide levels when administered concurrently, it is therefore recommended that patients treated concomitantly with ofloxacin and glibenclamide be monitored particularly closely. Since hypoglycaemia is then more likely to occur, close monitoring of blood sugar levels is recommended in such cases.

Cefixime

Anticoagulants

In common with other cephalosporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognised that a positive Coombs test may be due to the drug.

FERTILITY, PREGNANCY AND LACTATION

Ofloxacin

Pregnancy

Based on a limited amount of human data, the use of fluoroquinolones in the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcome. Animal studies have shown damage to the joint cartilage in immature animals but no teratogenic effects. Therefore ofloxacin should not be used during pregnancy.

Breast-feeding

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursing infant, breast feeding should be discontinued during treatment with ofloxacin.

Cefixime

Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine. There are no adequate and well-controlled studies in pregnant women. Cefixime should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Ofloxacin

Since there have been occasional reports of drowsiness/somnolence, impairment of skills, dizziness/vertigo and visual disturbances, which may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery), patients should know how they react to ofloxacin before they drive or operate machinery. These effects may be enhanced by alcohol.

Cefixime

In the case of side effects such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

UNDESIRABLE EFFECTS

Ofloxacin

The information given below is based on data from clinical studies and on extensive post marketing experience.

System organ class	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from available data)***
Infections and infestations	Fungal infection, Pathogen resistance			
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leucopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia
Immune system disorders		Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*	Anaphylactic shock*, Anaphylactoid shock*	
Metabolism and Nutrition disorders		Anorexia		Hypoglycaemia in diabetics treated with hypoglycaemic agents, Hyperglycaemia, Hypoglycaemic coma
Psychiatric disorders	Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt, Nervousness
Nervous system disorders	Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy*, Peripheral sensory motor neuropathy*, Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination	Tremor, Dykinesia, Ageusia, Syncope

Eye disorders	Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders	Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders		Tachycardia		Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders	Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudomembranous colitis*	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders		Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase), Blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe* Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders.
Skin and subcutaneous tissue disorders	Pruritus, Rash	Urticaria, Hot flushes, Hyperhidrosis Pustular rash	Erythema multiforme, Toxic epidermal necrolysis, Photo-sensitivity reaction*, Drug eruption, Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis	Stevens-Johnson syndrome, Acute generalised exanthemous pustulosis, Drug rash, Stomatitis Exfoliative dermatitis
Musculoskeletal and		Tendonitis	Arthralgia,	Rhabdomyolysis

connective tissue disorders			Myalgia, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral	and/or Myopathy, Muscular weakness, Muscle tear, Muscle rupture, Ligament rupture, Arthritis
Renal and urinary disorders		Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital, familial and genetic disorders				Attacks of porphyria in patients with porphyria
General disorders and administration site conditions				Asthenia, Pyrexia, Pain (including pain in back, chest and extremities)

* postmarketing experience

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- disturbances in attention
- disorientation
- agitation
- nervousness
- memory impairment
- Serious disturbances in mental abilities called delirium.

Cefixime
Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

The following adverse reaction (Preferred term# or equivalent) will be considered listed:

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia

	Thrombocytopenia Thrombocytosis
Gastrointestinal disorders:	Abdominal pain Diarrhoea* Dyspepsia Nausea Vomiting Flatulance
Hepatobiliary disorders:	Jaundice
Infections and infestations:	Pseudomembranous colitis
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased
Nervous system disorders:	Dizziness Headache Cases of convulsions have been reported with cephalosporins including cefixime (frequency not known)** Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment (frequency not known)**
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Renal and urinary disorders:	Renal failure acute including tubulointerstitial nephritis as an underlying pathological condition
Immune system disorders, administrative site conditions, skin and subcutaneous tissue disorders:	Anaphylactic reaction Serum sickness-like reaction Drug rash with eaosinophilia and systemic symptoms (DRESS) Pruritus Rash Drug Fever Arthralgia Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-oedema Urticaria Pyrexia Face oedema

	Genital pruritus Vaginitis

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

Preferred term in MedDRA (v.14.0)

*Diarrhoea has been more commonly associated with higher doses. Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Cefixime should be discontinued if marked diarrhoea occurs

** Cannot be estimated from available data

OVERDOSE

Ofloxacin

Symptoms

The most important signs to be expected following acute overdose are CNS symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures increases in QT interval as well as gastrointestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

Management

In the case of overdose steps to remove any unabsorbed ofloxacin e.g. gastric lavage, administration of adsorbants and sodium sulphate, if possible during the first 30 minutes, are recommended; antacids are recommended for protection of the gastric mucosa.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. A fraction of ofloxacin may be removed from the body with haemodialysis. Peritoneal dialysis and CAPD are not effective in removing ofloxacin from the body. No specific antidote exists.

Elimination of ofloxacin may be increased by forced diuresis.

Cefixime

There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics, including cefixime, particularly in case of overdose or renal impairment.

Adverse reactions seen at dose levels up to 2 g Cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Cefixime is not removed from the circulation in significant quantities by dialysis.

No specific antidote exists. General supportive measures are recommended.

CLINICAL PHARMACOLOGY
PHARMACODYNAMIC PROPERTIES
Ofloxacin
Pharmacotherapeutic group: Quinolone Antibacterials, Fluoroquinolones

ATC code: J01 MA 01

Mechanism of action

Ofloxacin inhibits bacterial DNA replication by inhibiting bacterial topoisomerases, particularly DNA gyrase and topoisomerase IV. It is active after oral administration.

Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous system.

The NCCLS MIC breakpoint recommendations are as follows:

S ≤ 2 mg/l and R ≥ 1 mg/l

Haemophilus influenzae and *Neisseria gonorrhoea* are exceptions with breakpoints at S ≤ 0.25 mg/l and R ≥ 1 mg/l

The BSAC general recommendations are S ≤ 2 mg/l and R ≥ 4 mg/l

According to DIN 58 940, the following limits apply for ofloxacin:

S ≤ 1 mg/L, I = 2 mg/L, R ≥ 4 mg/L.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilitieswhether micro-organisms will be susceptible to ofloxacin or not.

Only those pathogens relevant to the indications are listed.

	European range of acquired bacterial resistance to ofloxacin
Normally susceptible	
Aerobic Gram-positive micro organisms	
S. aureus - methicillin-sensitive	0.3-12.6%
S. pyogenes	2-5%
Aerobic Gram-negative micro organisms	
Acinetobacter spp	0.3-7.3%
Citrobacter spp.	3-15%
Enterobacter spp.	2-13%
E. coli	1-8%
H. influenzae	1%
Klebsiella spp.	1-10%
Moraxella spp.	0-0.2%

Morganella morganii	0-6.9%
N. gonorrhoeae	25%
Proteus spp.	1-15%
Serratia marcescens	2-2.4%
Others	
Chlamydia spp	
L. pneumophila	
Intermediately susceptible	
Aerobic Gram-positive micro organisms	
S. pneumoniae	70%
Providentia	17.1%
Aerobic Gram-negative micro organisms	
E. faecalis	50%
P. aeruginosa	20-30%
Serratia spp.	20-40%
Stenotrophomonas maltophilia	5.1-11%
Others	
Mycoplasma spp.	0-5.3%
Ureaplasma spp.	0-2.1%
Resistant	
Anaerobic bacteria	
S. aureus - methicillin-resistant	69.2-85.7%
T. pallidum	

Resistance

The main mechanism of bacterial resistance to ofloxacin involves one or more mutations in the target enzymes, which generally confer resistance to other active substances in the class. Efflux pump and impermeability mechanisms of resistance have also been described and may confer variable resistance to active substances in other classes.

Cefixime
Pharmacotherapeutic group: third generation cephalosporin, ATC code: J01DD08

Cefixime is an oral third generation cephalosporin which has marked in vitro bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative), *Branhamella catarrhalis* (beta-lactamase positive and negative) and *Enterobacter* species. It is highly stable in the presence of beta-lactamase enzymes.

Most strains of enterococci (*Streptococcus faecalis*, group D Streptococci) and Staphylococci (including coagulase positive and negative strains and meticillin-resistant strains) are resistant to cefixime. In addition, most strains of *Pseudomonas, Bacteroides fragilis, Listeria monocytogenes* and *Clostridia* are resistant to cefixime.

PHARMACOKINETIC PROPERTIES

Ofloxacin

Absorption

The administration of oral doses to fasting volunteers was followed by a rapid and almost complete absorption of ofloxacin. The peak plasma concentration after a single oral dose of 200mg averaged 2.6 µg/ml and was reached within one hour. The plasma elimination half-life was 5.7 to 7.0 hours and was not dose related.

Distribution

The apparent distribution volume was 120 litres. The plasma concentration did not materially rise with repeat doses (accumulation factor for twice daily dosage: 1.5). The plasma protein binding was approx. 25%.

Biotransformation

The biotransformation of ofloxacin was below 5%. The two main metabolites found in the urine were N-desmethyl-ofloxacin and ofloxacin-N-oxide.

Elimination

Excretion is primarily renal. Between 80 and 90% of the dose were recovered from the urine as unchanged substance.

Ofloxacin was present in the bile in glucuronidised form. The pharmacokinetics of ofloxacin after intravenous infusion are very similar to those after oral doses. The plasma half-life is prolonged in persons with renal insufficiency; total and renal clearance decrease in accordance with the creatinine clearance. In renal insufficiency the dose should be reduced.

No clinically relevant interactions were seen with food and no interaction was found between ofloxacin and theophylline.

Cefixime

The absolute oral bioavailability of cefixime is in the range of 22-54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

From in vitro studies, serum or urine concentrations of 1 mcg/mL or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mcg/mL. Little or no accumulation of cefixime occurs following multiple dosing.

The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean Cmax and AUC

values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.

Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations which are not seen following clinical dosing.

Transfer of 14C-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placetal transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

PRECLINICAL SAFETY DATA

Ofloxacin

Preclinical effects in conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, reproductive studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Joint toxicity was observed at exposure in the human therapeutic range in juvenile rats and dogs. Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses.

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. However, like some other quinolones Ofloxacin is phototoxic in animals at exposure in the human therapeutic range. The phototoxic, photomutagenic and photocarcinogenic potential of ofloxacin is comparable with that of other gyrase inhibitors.

Preclinical data from conventional genotoxicity studies reveal no special hazard to humans, carcinogen potential has not be investigated.

Reproduction toxicity

Ofloxacin has no effect on fertility, peri- or postnatal development, and therapeutic doses did not lead to any teratogenic or other embryotoxic effects in animals. Ofloxacin crosses the placenta and levels reached in the amniotic fluid are about 30% of the maximal concentrations measured in maternal serum.

EXPIRY DATE:

Do not use later than date of expiry

STORAGE

Store in a cool and dry place, away from light.
Keep all medicines out of the reach of children

PRESENTATION
CEFIPOWER is available in strip of 10 tablets.

MARKETED BY


TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

IN/ CEFIPOWER 200,200 mg/JAN-19/01/PI