SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ofloxacin 200mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of ofloxacin.

Excipients with known effect
Each tablet contains 105.6 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets

White, round film-coated tablets, 11 mm diameter, scored on both sides. One side of the tablet is debossed "FXN" on one side of the breakline and "200" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection;
- other first-line antibiotics are contraindicated in an individual patient;
- other first-line antibiotics have caused side effects requiring treatment to be stopped;
- treatment with other first-line antibiotics has failed.

Ofloxacin is indicated for the treatment of the following infections when caused by sensitive organisms (see section 5.1.):

- Uncomplicated acute cystitis
- Acute pyelonephritis
- Complicated urinary tract infections
- Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis
- Community-acquired pneumonia
- Gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoea
- Non-gonococcal urethritis and cervicitis;
- Complicated skin and soft tissue infections

Consideration should be given to official guidance on the appropriate use of anti-bacterial agents.

4.2. Posology and Method of Administration

Posology

General dosage recommendations:
The dose of ofloxacin should be 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. 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.

Indications	**Single and daily doses**	**Usual duration of therapy**
Uncomplicated lower urinary tract infections	200 – 400 mg daily	3 days
Complicated infections of the kidneys and urinary tract	400 mg daily, increasing if necessary, to 400 mg twice a day	7-10 days
Acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis Community-acquired pneumonia	400mg daily, increasing, if necessary, to 400 mg twice a day	7-10 days
Gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae	400 mg	Single dose
Non-gonococcal urethritis and cervicitis	400 mg daily	7-10 days
Complicated Skin and soft tissue infections	400 mg twice a day	7-10 days

Renal impairment:
In patients with impaired renal function, the following oral or I.V dosages are recommended:

Creatinine clearance	*Unit dose mg**	*Number /24 hours*	*Intervals hours*
50 - 20 ml/min	100 – 200	1	24
< 20 ml/min** Or haemodialysis or peritoneal dialysis	100 or 200	1 1	24 48

* According to indication or dose interval

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

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:

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

or

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

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

Hepatic impairment (e.g. cirrhosis with ascites)
It is recommended that a maximum daily dose of 400 mg of ofloxacin be not exceeded, because of possible reduction of excretion.

Elderly:
Age in itself does not impose to adapt the dosage of ofloxacin. However, special attention to renal and liver function should be paid in elderly patients, and the dosage should be adapted accordingly (see section 4.4).

Paediatric population:
Ofloxacin is not indicated for use in children or growing adolescents.

Type and duration of treatment:
A daily dose of up to 400mg 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 400mg must be divided into two separate doses and be given at approximately equal intervals.

Duration of treatment is dependent on the severity of the infection and the response to treatment.
The usual durations of treatment are stated in the table.

In some instances, a minimum of 5 days treatment may be sufficient.

Treatment should not exceed 2 months duration.

Method of administration

Ofloxacin Tablets should be swallowed with sufficent amount of liquids. They may be taken on an empty stomach or with meals. Concomitant administration with antacids should be avoided (see section 4.5).

4.3. Contra-Indications

Ofloxacin must not be used

- in patients hypersensitive to ofloxacin, other quinolones, or any of the excipients
- in patients with history of epilepsy or with any existing central nervous system disorder that is associated with a lower seizure threshold
- in patients with history of tendon disorders related to fluoroquinolone administration
- in children or adolescents in the growth phase*
- during pregnancy*
- in breast-feeding women*

*because, judging from animal experiments, a risk of damage to the growth-plate cartilage in the growing organism cannot be entirely excluded.

Ofloxacin should not be given to patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity because they are prone to haemolytic reactions when treated with quinolone antibacterial agents.

4.4 Special warnings and precautions for use

- *Prolonged, disabling and potentially irreversible serious adverse drug reactions*

  Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

- The use of ofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with ofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

- 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 (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

- 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. The physician should inform the patient of this risk.

- Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplama, or angina tonsillaris caused by β-haemolytic Streptococci.

- *Clostridium difficile*-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or up to 10 weeks after treatment with Ofloxacin Tablets, may be a symptom of *Clostridium difficile* enterocolitis, the most severe form being pseudomembraneous colitis (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with ofloxacin. If pseudo-membranous colitis is suspected, ofloxacin must be stopped immediately.

Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Medicinal products that inhibit peristalsis are contra-indicated 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 of epilepsy (see section 4.3) and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

Such patients may be patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5).

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

- *Tendinitis and tendon rupture*

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those

treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with ofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

- Patients with renal impairment

Since ofloxacin is mainly excreted by the kidneys, the dose of ofloxacin should be adjusted in patients with renal impairment (see section 4.2).

- 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 (see section 4.8). 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 hepatic impairment

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, pruritis or tender abdomen (see section 4.8).

- 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 (see section 4.5).

- 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.

- Prevention of photosensitisation

Photosensitisation has been reported with ofloxacin (see section 4.8). It is recommended that patients should avoid strong sunlight or artificial UV radiation (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation

- Superinfection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms, especially enterococci, resistant strains of some organisms or candida. Repeated evaluation of the patient's condition is essential. If secondary infection occurs during therapy,, appropriate and alternative treatment should be given.

- **Cardiac disorders**

QT interval prolongation

Very rare cases of QT interval prolongation 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. hypokalaemia, hypomagnesaemia)
- congenital long QT syndrome
- acquired QT prolongation
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

(See also section 4.2, section 4.5, section 4.8 and section 4.9).

- Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease or in presence of other risk factors or conditions predisposing.

for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally

-for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally

-for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

- 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.

- *Peripheral neuropathy*

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).
- Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with a 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.

Ofloxacin should therefore be administered with caution in such patients.

- Vision disorders:

  If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

- Interference with laboratory tests:

  Determination of opiates or porphyrins in urine may give false-positive results during treatment with ofloxacin. It may be necessary to confirm positive opiate or porphyrin screens by more specific methods.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

During prolonged therapy (more than two weeks and up to two months), regular monitoring of haematological parameters and blood chemistry is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids, Sucralfate, Metal Cations:
Antacids containing aluminium (including sucralfate) and magnesium hydroxides, aluminium phosphate, zinc, iron, are liable to reduce the absorption of ofloxacin tablets. Ofloxacin should be administered approximately 2 hours apart from antacids.

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 anti-inflammatory drugs, or other agents, which lower the seizure threshold. However, ofloxacin does not cause any relevant changes in theophylline plasma concentrations.

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, antipsychotics) (see section 4.4).

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 be monitored in patients treated with vitamin K antagonists (see section 4.4) because of a possible increase in the effect of coumarin derivatives.

Glibenclamide:
Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; it is therefore recommended that patients treated with this combination should be closely monitored as hypoglycaemia is more likely to occur.

Probenecid, cimetidine, furosemide, or 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.

4.6. Fertility, pregnancy and Lactation

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 (see section 4.3).

The safety of this medicinal product for use in human pregnancy has not been established. Reproduction studies performed in rats and rabbits did not reveal any evidence of teratogenicity, impairment of fertility or impairment of peri- and post-natal development. However, as with other quinolones, ofloxacin has been shown to cause arthropathy in immature animals.

Breast-feeding

Studies in rats have indicated that ofloxacin is secreted in milk.

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 (see section 4.3).

4.7. Effects on Ability to Drive and Use Machines

Some adverse reactions (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patients 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.

4.8 Undesirable effects

The overall frequency of adverse reactions from the clinical trial data base is about 7%. The commonest events involved the gastrointestinal system (about 5.0%) and the nervous system (about 2.0%).

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10,000), not known (cannot be estimated from the available data) including isolated reports.

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

System organ class	**common (≥ 1/100 to < 1/10)**	**uncommon (≥ 1/1000 to < 1/100)**	**rare (≥1/10,000 to < 1/1000)**	**very rare (< 1/10, 000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations		fungal infection, pathogen resistance			

Blood and lymphatic system disorders				anaemia, haemolytic anaemia, leucopenia, eosinophilia, thrombocyto-penia	agranulocytosis, bone marrow failure Bone marrow failure may lead to pancytopenia
Immune system disorders			anaphylactic reaction[a], anaphylactoid reaction[a], angioedema[a]	anaphylactic shock[a], anaphylactoid shock [a]	
Metabolism and nutrition disorders			anorexia		Hypoglycaemia in diabetics treated with Hypoglycaemic agents (see section 4.4) Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders*		restlessness, sleep disorder, agitation, insomnia	psychotic disorder (for e.g. hallucination), anxiety, confusional state, nightmares, depression, delirium	abnormal dreams, psychotic behaviour	psychotic disorders and depression with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4) Nervousness
Nervous system disorders*		headache, dizziness	somnolence, paraesthesia, dysgeusia, parosmia	peripheral sensory neuropathy[a], peripheral sensory motor neuropathy[a], convulsion[a], extra-pyramidal symptoms or other disorders of muscular coordination.	Tremor, Dyskinesia, Ageusia, Syncope
Eye disorders*		eye irritation	visual disturbances (e.g. double vision, blurred vision)	allergic conjunctivitis	Uveitis
Ear and labyrinth disorders*		vertigo		tinnitus, hearing loss	Hearing impaired

Cardiac disorders**			Tachycardia		ventricular arrhythmias, 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**			Hypotension	circulatory collapse, flushing	
Respiratory, thoracic and mediastinal disorders		cough, nasopharyngitis	dyspnoea, bronchospasm		allergic pneumonitis, severe dyspnoea
Gastrointestinal disorders		nausea, vomiting, diarrhoea, abdominal pain	enterocolitis, sometimes haemorrhagic	Pseudomembr-anous colitis[a]	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders			hepatic enzymed increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatas), blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe[a] Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders (see section 4.4).
Skin and subcutaneous tissue disorders		rash, pruritus	urticaria, hot flushes, hyperhidrosis, pustular rash	toxic epidermal necrolysis, photosensitivit y reaction[a], drug eruption, vascular purpura, vasculitis, which can lead in exceptional cases to skin necrosis, vesiculobullous rash, angioedema erythema multiforme	Stevens-Johnson syndrome, acute generalised exanthemous pustulosis, drug rash Stomatitis; Exfoliative dermatitis

Musculoskeletal and connective tissue disorders*			Tendinitis, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral	arthralgia, myalgia,	muscle weakness, rhabdomyolysis and/or myopathy, muscle tear, muscle rupture Ligament rupture, Arthritis
Renal and urinary disorders			serum creatinine increased	renal function disorder, acute renal failure	acute interstitial nephritis
Congenital and familial/ genetic disorders					attacks of prophyria in patients with prophyria
General disorders and administration site conditions*				unsteady gait	Asthenia Pyrexia Pain (including pain in back, chest, and extremities)

[a] postmarketing experience

* Cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, fatigue, psychiatric symptoms, memory impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Except in very rare instances (e.g. isolated cases of smell, taste and hearing disorders) the adverse effects observed subsided after discontinuation of ofloxacin.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9. Overdose

Symptoms of overdose
The most important signs to be expected following acute overdose are CNS symptoms such as confusion, dizziness, impairment of consciousness and 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

Treatment of overdose
In the event of overdose symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.
In the case of overdose steps to remove any unabsorbed ofloxacin eg 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. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Mode of action
Pharmacotherapeutic group: fluoroquinolones
ATC code: J01 MA 01
Ofloxacin inhibits bacterial DNA replication in a range of gram-positive and gram-negative pathogenic bacteria by inhibiting bacterial topoisomerases, particularly DNA gyrase and topoisomerase IV.

The NCCLS MIC breakpoint recommendations are as follows :
S ≤ 2 mg/l and R ≥ 8 mg/l
Intermediate susceptibility at 4 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 probabilities whether 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	

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.

5.2. Pharmacokinetic Properties

Absorption:

Ofloxacin is absorbed rapidly and almost completely when administered to fasting volunteers. The mean peak plasma concentration following a single oral dose of 200 mg is 2.6 µg/ml and is achieved within an hour. The plasma concentration does not increase significantly with multiple dosing (accumulation factor with twice daily dosage: 1.5).

Distribution:
The apparent volume of distribution is 120 litres. Plasma protein binding is approximately 25%.

Biotransformation:
Ofloxacin is less than 5% biotransformed. The two principal metabolites found in the urine are N-desmethyl-ofloxacin and ofloxacin-N-oxide. Ofloxacin is found as the glucuronide in the bile.

Elimination:
Elimination is primarily by the renal route in that 80 to 90 % of the dose is excreted unchanged in the urine. The plasma elimination half-life is 5.7 to 7.0 hours, irrespective of dose.

Patients with renal impairment:
The plasma elimination half-life is prolonged in individuals with impaired renal function; total and renal clearance decrease in accordance with creatinine clearance.

5.3. Pre-clinical Safety Data

Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses. Aside from this, preclinical studies with single and repeated use in adult animals as well as safety pharmacological investigations, yielded no indications of further specific risks in connection with the administration of ofloxacin.

Like other gyrase inhibitors, ofloxacin can also cause damage to large weight-bearing joints of juvenile animals during the growth period. The extent of the cartilage damage caused is dependent on age, species, and dose. In addition, stress relief of the joints considerably reduces cartilage damage.

Ofloxacin has no influence on fertility or perinatal and postnatal development and has no teratogenic or other embryotoxic effects in animal experiments, if administered at therapeutic doses.

Ofloxacin has not been evaluated in long-term carcinogenicity studies. In-vitro and in-vivo studies showed that ofloxacin is not mutagenic. Phototoxicity, photomutagenicity, and photocarcinogenicity data of ofloxacin indicate only slight photomutagenic and phototumorigenic effects in vitro and/or in vivo, as compared to other fluoroquinolones.

There are no indications of cataractogenic or co-cataractogenic effects following exposure to ofloxacin.

Preclinical investigations performed with ofloxacin have, to date, demonstrated only a slight QT-prolonging potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose monohydrate
Pregelatinised starch
Hypromellose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Titanium dioxide E171
Macrogol 3000
Triacetin.

6.2. Incompatibilities

Not applicable

6.3. Shelf-Life

3 years

6.4. Special Precautions for Storage

Keep blister in the outer carton.

6.5. Nature and Content of Container

Transparent PVC/PVdC-aluminium blisters / white opaque PVC/PVdC-aluminium blisters
Blister packs of 10, 14, 20 and 50 tablets

Not all pack sizes may be marketed.

6.6. Instruction for Use, Handling and Disposal

No special requirements

7. Marketing Authorisation Holder

Teva UK Limited,
Ridings Point, Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0353

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/04/2009

10 DATE OF REVISION OF THE TEXT

21/11/2023