SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ofloxacin 200mg Tablets
Ofloxacin 400mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of ofloxacin.
Each tablet contains 400 mg of ofloxacin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets (tablet)

The tablets are white capsule shaped and scored on both sides with 'BL' and '200' debossed on one face of the tablet.

The tablets are white capsule shaped and scored on both sides with 'BL' and '400' debossed on one face of the tablet.

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 in adults for the treatment of the following bacterial infections if these are caused by pathogens sensitive to ofloxacin (see sections 4.4 and 5.1):

- Acute pyelonephritis and complicated urinary tract infections
- Bacterial prostatitis, epididymo-orchitis
- Pelvic inflammatory disease, in combination with other antibacterial agents
- Upper and lower urinary tract infections
- Gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae
- Non gonococcal urethritis and cervicitis
- Uncomplicated cystitis
- Urethritis
- Complicated skin and soft-tissue infections
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis
- Community acquired pneumonia

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

4.2 Posology and method of administration

Posology

General dosage recommendations: 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. 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.

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.

Lower urinary tract infection: 200-400mg daily.

Upper urinary tract infection: 200-400mg daily increasing, if necessary, to 400mg twice a day.

Acute exacerbation of chronic bronchitis, community acquired pneumonia: 400 mg daily increasing, if necessary, to 400mg twice daily.

Non-gonococcal cervicitis: 400mg daily in single or divided doses.

Complicated skin and soft tissue infections: 400 mg twice daily.

Indication	**Daily dose regimen** *(according to severity)*	**Duration of treatment** *(according to severity)*
Complicated UTI	200 mg twice daily (can be increased up to 400 mg twice daily)	7-21 days
Acute Pyelonephritis	200 mg twice daily (can be increased up to 400 mg twice daily)	7-10 days (can be extended up to 14 days)
Acute prostatitis Chronic prostatitis	200 mg twice daily (can be increased up to 400 mg twice daily)	2-4 weeks* 4-8 weeks*
Epididymo-orchitis	200 mg twice daily (can be increased up to 400 mg twice daily)	14 days
Pelvic inflammatory disease	400 mg twice daily	14 days
Uncomplicated cystitis	200 mg twice daily or 400 mg once daily	3 days 1 day
Complicated cystitis	200 mg twice daily	7-14 days
Non-gonococcal urethritis	300 mg twice daily	7 days
Neisseria gonorrhoeae urethritis See section 4.4	400 mg single dose	1 day
Gastroenteritis	200 mg twice daily	
Abdominal infections	200 mg twice daily	
ENT infections and chronic respiratory tract infections	200 mg twice daily	
Acute exacerbations of chronic obstructive pulmonary	500 mg once daily	7–10 days

disease, including bronchitis		
Cystic fibrosis	400 mg once daily (can be increased up to 400 mg twice daily)	

*For prostatitis, extension of treatment can be considered after careful re-examination of the patient.

A single dose of 400 mg of ofloxacin is sufficient for the treatment of gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae.*

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	Creatinine Level	Posology
20 to 50ml/min	1.5 to 5 mg/dL	100mg – 200mg/24hr
<20 mL/min**	>5 mg/dl	100mg every 24hr
Haemodialysis or peritoneal dialysis		100mg every 24 hr

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). 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 function should be paid in elderly patients, and the dosage should be adapted accordingly. (See section 4.4 QT interval prolongation).

***Children*:** Ofloxacin is not indicated for use in children or growing adolescents (see section 4.3).

***Duration of treatment*:**
The duration of treatment with Ofloxacin varies between 7 and 10 days depending on the susceptibility of the organism, severity of infection and clinical course. As with other antibiotics, it is recommended to continue treatment for an additional 3 days after the symptoms have disappeared.
The maximum daily dose is 800 mg.

Method of administration

For oral use.

Ofloxacin tablets can also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous ofloxacin.

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 (see section 4.5).

4.3 Contraindications

The use of ofloxacin is contraindicated as follows:

- Hypersensitivity to the active substance, to any other fluoroquinolone antibacterials, or to any of the excipients listed in section 6.1.
- In patients with a history of epilepsy or in patients predisposed to seizures due to pre-existing central nervous system disorders, such as craniocerebral trauma, central nervous system inflammation or cerebral infarction.
- 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.
- Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be 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).

Ofloxacin is not the drug of first choice in pneumonia caused by *Streptococcus pneumoniae* or *Chlamydia pneumoniae*.

Methicillin-resistant *S. aureus*

Methicillin-resistant *S. aureus* is 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.

***Streptococcus pneumoniae*, β-haemolytic Streptococci and Mycoplasma**

Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplasma or infection caused by β-haemolytic Streptococci.

***Neisseria gonorrhoeae* infections**

Due to increase in resistance to *N. gonorrhoeae*, ofloxacin should not be used as empirical treatment option in suspected gonococcal infection (urethral gonococcal

infection, pelvic inflammatory disease and epididymo-orchitis), unless the pathogen has been identified and confirmed as susceptible to ofloxacin. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Pelvic inflammatory disease

For pelvic inflammatory disease, ofloxacin should only be considered in combination with anaerobe coverage.

Hypersensitivity and allergic reactions

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.

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.

Diseases caused by *Clostridioides difficile*

Diarrhoea, particularly if severe, persistent and/or bloody, occurring during or after treatment with ofloxacin (including several weeks after treatment), may be symptomatic of pseudomembranous colitis (*Clostridioides difficile* - associated diarrhoea - CDAD). CDAD may range in severity from mild to life threatening, the most severe form 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, treatment with ofloxacin must be stopped immediately.

Specific targeted antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products that inhibit peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history of epilepsy or with a known predisposition to seizures (see section 4.3) and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed 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 (see section 4.5: Interactions).

In case of convulsive seizures, treatment with ofloxacin should be discontinued (see section 4.5).

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. The daily dose should be adjusted in elderly patients based on creatinine clearance (see section 4.2). Close monitoring of these patients is therefore necessary if they are prescribed ofloxacin.

All patients should consult their physician if they experience symptoms of tendonitis. 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).

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:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including Ofloxacin, in these populations.

(See section 4.2 *Elderly*, 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 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.

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 behaviour including suicide attempt, sometimes after a single dose (see section 4.8). In the event that a patient develops these reactions, ofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice.
Alternative non-fluoroquinolone antibacterial therapy should be considered, 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, pruritis or tender abdomen. (See section 4.8: Undesirable effects)

Patients treated with vitamin K antagonists

Due to possible increase in coagulation tests (PT [prothrombin time]/INR [International Normalised Ratio]) 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 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.

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 and periodic *in vitro* susceptibility tests may be useful. If secondary infection occurs during therapy, appropriate measures should be taken.

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).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hyperglycaemia

and hypoglycaemia have been reported more frequently in the elderly, 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 (see section 4.8).

Ofloxacin treatment should be stopped immediately if a patient reports disturbance in blood glucose, and alternative non-fluoroquinolone antibacterial therapy should be considered.

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.

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

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 method.
Cross-resistance with various quinolones has been shown.

Important information regarding the ingredients in this medicine

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

4.5 Interaction with other medicinal products and other forms of interaction

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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (See section 4.4 QT interval prolongation).

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

Prolongation of bleeding time has been reported during concomitant administration of Ofloxacin and anticoagulants.

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

Glibenclamide
Interaction with antidiabetic drugs has been reported. 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.

Probenecid, cimetidine, furosemide and methotrexate
Probenecid decreased the total clearance of ofloxacin by 24%, and increased AUC by 16%. It acts at renal level by competing or inhibiting the active transport that forms the basis for tubular section. Caution should be exercised when ofloxacin is co-administered with drugs that affect the tubular renal secretion such as probenecid, cimetidine, furosemide and methotrexate. Especially when using high doses, the concomitant use of quinolones with other drugs undergoing tubular excretion, the excretion of the two drugs may diminish, which leads
to increased serum concentrations.

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 because of a possible increase in the effect of coumarin derivatives (see section 4.4).

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

(see section 5.3). Therefore, ofloxacin should not be used during pregnancy. (See section 4.3: Contraindications)

Breast-feeding
Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the newborn, breast feeding should be discontinued during treatment with ofloxacin. (See section 4.3: Contraindications)

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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 (≥1/1,000 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		Overgrowth of non-susceptible microorganisms incl. Fungi, Pathogen resistance			
Blood and lymphatic system disorders				Anaemia, Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia

Immune system disorders			Anaphylactic reaction***, Anaphylactoid reaction***, Angioedema***	Anaphylactic shock***, Anaphylactoid shock***	
Metabolism and Nutrition disorders			Anorexia, Hypoglycaemic coma		Hypoglycaemia in diabetics treated with hypoglycaemic agents (see Section 4.4), Hyperglycaemia
Psychiatric disorders *		Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression, Delirium		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt (see Section 4.4) Nervousness
Nervous system disorders *		Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia, Memory impairment	Peripheral sensory neuropathy *** Peripheral sensory motor neuropathy*** Convulsion***, Extra-pyramidal symptoms or other disorders of muscular coordination	Tremor Dyskinesia Ageusia Syncope Benign intracranial hypertension (Pseudotumor cerebri).
Eye disorders *		Eye irritation	Visual disturbance		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 **	*applies only to the solution for infusion:* Phlebitis		Hypotension		*applies only to the solution for infusion:* During infusion of ofloxacin, tachycardia and hypotension may occur. Such a decrease in blood pressure may, in very rare cases, be severe.
Respiratory, thoracic and mediastinal disorders		Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis (pneumonia), Severe dyspnoea
Gastrointestinal disorders		Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudomembranous colitis***	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders			Hepatic enzymes increased (ALT, AST, 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 (see section 4.4).
Skin and subcutaneous tissue disorders		Pruritus, Rash	Urticaria, Hot flushes, Hyperhidrosis Pustular rash	Erythema multiforme, Toxic epidermal necrolysis, Photosensitivity reaction***, Drug eruption Vascular	Stevens-Johnson syndrome; Acute generalized exanthemous pustulosis; drug rash; Stomatitis, Exfoliative

				purpura, Vasculitis, which can lead in exceptional cases to skin necrosis (vasculitis presents generally with petechiae, bleeding vesicles and small pimples with scabs and may even affect internal organs)	dermatitis
Musculoskeletal and Connective tissue disorders *			Tendinopathies Tendon rupture (e.g. Achilles tendon), Tendonitis as is the case with fluoroquinolones, this effect may occur within 48 hours of treatment start and may be bilateral.	Arthralgia, Myalgia,	Rhabdomyolysis 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*	*applies only to the solution for infusion:* Infusion site reaction (pain, reddening)				Asthenia Pyrexia Pain (including pain in back, chest, and extremities)

*Very rare 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 tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia and neuralgia, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration 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).

*** post-marketing experience

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

4.9 Overdose

Symptoms

The most important signs to be expected following acute overdosage are CNS symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures, increases 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 event of an overdose, it is possible to remove the unabsorbed ofloxacin from the body with gastric lavage by administering and adsorbents and sodium sulphate during the first 30 minutes after the overdose. 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.

No specific antidote for Ofloxacin exists, but, as ofloxacin is excreted renally, it is possible to remove the already absorbed drug by forced diuresis.

Haemodialysis and peritoneal dialysis are not useful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Quinolone Antibacterials, Fluoroquinolones.
ATC code J01M A01.

Mechanism of action
This medicinal product contains ofloxacin, a broad-spectrum anti-infective agent that belongs to the fluoroquinolones group. Ofloxacin acts on both Gram-positive and Gram-negative bacteria.

Resistance
Resistance to ofloxacin is acquired in a multi-step process at the target site through mutations in the two type II topoisomerases, DNA gyrase and topoisomerase IV. Other mechanisms of resistance such as permeability barriers (common in *Pseudomonas aeruginosa*) and efflux systems may also influence susceptibility to ofloxacin.

The prevalence of resistance may vary based on geographical and temporal data for a given species. It is recommended that information about local resistance be obtained, in particular for the treatment of serious infections. If necessary, the opinion of an expert can be requested when the local prevalence of resistance is such that the usefulness of the product is uncertain, at least for certain types of infections.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ofloxacin and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

PK-PD relationship
Fluoroquinolones have a dose-dependent bactericidal activity with a moderate post-antibiotic effect. For this class of antibiotics, the ratio between the area under the curve (AUC) and the

minimum inhibitory concentration (MIC) or between the maximum concentration (Cmax) and the MIC is predictive of clinical success.

Bacteriological activity

The following pathogens may be considered susceptible:

- *Methicillin-susceptible Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Escherichia coli*
- *Klebsiella*
- *Enterobacter, Citrobacter*
- *Proteus (indole-negative and indole-positive)*
- *Salmonella, Shigella*
- *Yersinia enterocolitica*
- *Campylobacter jejuni*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Hafnia spp.*
- *Aeromonas spp.*
- *Plesiomonas spp.*
- *Chlamydiae*
- *Legionella pneumophila.*

Moderately susceptible bacteria include:

- *Serratia marcescens*
- *Enterococcus faecium*
- *Clostridium tetani*
- *Enterococci*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter*
- *Mycoplasma pneumoniae*
- *Streptococcus viridans*
- *Mycoplasma hominis*
- *Mycobacterium tuberculosis*
- *Mycobacterium fortuitum.*

Bacteria that can be considered resistant:

- *Fusobacterium spp.*
- *Eubacterium spp.*
- *Peptococci*
- *Peptostreptococci*
- *Treponema pallidum*
- *Clostridium difficile*
- *Nocardia asteroids*
- *Bacteroides spp.*
- *Ureaplasma urealyticum.*

In the case of urinary tract infection, an MIC < 16 µg/mL can still be considered susceptible.

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

5.2 Pharmacokinetic properties

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 200 mg averaged 2.6 µg/ml and was reached within one hour. The plasma elimination half-life was 5.7 to 7 hours and was not dose related.

Distribution

The maximum serum concentrations after administration of a single 200 mg oral dose reach a mean of 2.5 to 3 µg/mL after 1 hour.

For 12 to 24 hours, serum concentrations remain greater than the MIC for most ofloxacin susceptible bacteria (see list above).

Ofloxacin has good tissue penetration, which allows it to reach tissue concentrations equal to or even higher than serum levels after a single administration. The apparent volume of distribution is 120 L.
The protein binding rate of ofloxacin is about 25%.

Dose	Cmax (µg/mL) - p.o.	Tmax (h) - p.o.
100 mg	1.0-1.3	0.5-1.6
200 mg	2.6	0.8-1.0
300 mg	3.4-3.8	0.8-1.2
400 mg	3.5-5.3	1.1-1.4

During a study, the following mean plasma concentrations were observed after oral administration of a single 200-mg and 400-mg dose of ofloxacin:

Dose	Mean plasma concentrations (µg/mL)					
	1h	2h	4h	8h	12h	24h
200 mg	2.27	1.44	1.06	0.64	0.42	0.12
400 mg	4.50	3.24	2.35	1.45	0.96	0.30

After several administrations, the serum concentration does not increase significantly (about x 1.5).
Concentrations of ofloxacin in the urine and at the urinary tract infection site exceed those Measured in the serum by a factor of 5 to 100.

Biotransformation

The serum elimination half-life is 6 to 7 hours and is linear.

Elimination
Excretion is primarily renal.
Ofloxacin is excreted almost entirely in the urine, unchanged (less than 5% is found as metabolites).
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.

5.3. Preclinical safety data

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 been 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycolate
Hydroxypropyl cellulose
Magnesium stearate
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

Ofloxacin 200mg Tablets are available in blister packs of 10, 20 and 100 tablets in Alu/PVC blisters.

6.6 Special precautions for disposal

Not special requirements

7. MARKETING AUTHORISATION HOLDER

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