SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OFLOCET 200 mg, film-coated, scored tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ofloxacin ..... 200.000 mg
Per film-coated, scored tablet.
Excipient(s) with known effect: lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet, round, biconvex, with a score line on one side and engraved "200" on the other.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

OFLOCET 200 mg, film-coated, scored tablet is indicated for the treatment of the following bacterial infections (see sections 4.4 and 5.1). Particular attention should be paid to available information on bacterial resistance to ofloxacin before initiating treatment.
Official guidelines regarding the appropriate use of antibacterial agents should be taken into account.

<u>In adults</u>

- **Acute pyelonephritis and complicated urinary tract infections**
- **Bacterial prostatitis, orchiepididymitis**
- **Pelvic inflammatory disease, in combination with other antibiotics**
- **For the infections listed below, OFLOCET should be used only when antibiotics usually recommended for the treatment of these infections are considered inappropriate:**
    - **Uncomplicated acute cystitis**
    - **Urethritis**
    - **Bone and joint infections**
    - **Complicated skin and soft tissue infections**
    - **Acute bacterial sinusitis**
    - **Acute exacerbation of chronic obstructive pulmonary disease, including chronic bronchitis**
    - **Community-acquired pneumonia**

<u>Special situations</u>
Anthrax inhalation: post-exposure prophylaxis and curative treatment

During treatment of infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, the emergence of resistant mutants has been reported and may justify combination therapy with another antibiotic. Microbiological monitoring to detect such resistance should be considered, particularly when treatment failure is suspected.
The use of ofloxacin is not recommended in severe infections, especially bacteraemia caused by *Pseudomonas aeruginosa* or *Acinetobacter*.

4.2. Posology and method of administration

Posology

Adults
In patients with normal renal function
400 mg/day in two doses (i.e. 1 tablet morning and evening).

- **For the treatment of bronchial suppuration, the dosage is 400 mg/day as a single dose.**
- **This dosage may be increased up to 600 mg or 800 mg/day in patients with high body weight and/or in cases of severe infections, particularly in immunocompromised patients or in nosocomial infections caused by multidrug-resistant Gram-negative bacteria such as *Pseudomonas*, *Acinetobacter*, and *Serratia*.**
  For these pathogens, as well as for *Staphylococcus aureus*, combination with another antibiotic appropriate for the causal organism is recommended.

Indication	Daily dosage (depending on severity)	Duration of treatment (depending on severity)
Complicated cystitis	200 mg twice daily (may be increased to 400 mg twice daily)	7–21 days
Acute pyelonephritis	200 mg twice daily (may be increased to 400 mg twice daily)	7–10 days (may be extended to 14 days)
Acute bacterial prostatitis	200 mg twice daily (may be increased to 400 mg twice daily)	2–4 weeks*
Chronic bacterial prostatitis	200 mg twice daily (may be increased to 400 mg twice daily)	4–8 weeks
Orchiepididymitis	200 mg twice daily (may be increased to 400 mg twice daily)	14 days
Pelvic inflammatory disease	400 mg twice daily	14 days
Uncomplicated acute cystitis	200 mg twice daily **or** 400 mg once daily (See MONOFLOCET)	3 days / 1 day
Non-gonococcal urethritis	300 mg twice daily	7 days
Urethritis due to *Neisseria gonorrhoeae* (see section 4.4)	400 mg as a single dose	1 day

For bacterial prostatitis, a longer treatment duration may be considered after a careful reassessment of the patient.
OFLOCET may also be used as a follow-up to initial intravenous ofloxacin therapy in patients whose clinical condition has improved.

Special situations

Anthrax disease: post-exposure prophylaxis and curative treatment in symptomatic individuals who can receive oral therapy, either immediately or after switching from parenteral therapy: **800 mg/day in two divided doses**.

The treatment duration is **8 weeks** when exposure to anthrax is confirmed.

Elderly patients

Age alone does not require dose adjustment of ofloxacin. However, the dosage must be adapted according to the degree of renal impairment (see section 4.4 QT interval prolongation).

Patients with renal impairment

Dose adjustment must be made according to the degree of renal insufficiency by spacing administrations:

- **Mild to moderate renal impairment** (creatinine clearance > 20 ml/min): **200 mg once every 24 hours**.
- **Severe renal impairment** (creatinine clearance ≤ 20 ml/min): **200 mg once every 48 hours** or **100 mg once every 24 hours**.

It is recommended to monitor serum levels of the active substance in renally impaired or haemodialysed patients.

Patients with hepatic impairment (e.g., cirrhosis with ascites)

It is recommended **not to exceed a maximum daily dose of 400 mg** of ofloxacin due to possible decreased elimination.

Paediatric population

In exceptional cases of severe infections (see sections 4.3 and 4.4), the following dosing regimen may be used:

10–15 mg/kg/day in two daily doses, without exceeding **400 mg/day** in two doses.

Method of administration

Oral use.

Tablets should be swallowed with a large glass of water.

They may be taken on an empty stomach or with food.

OFLOCET should **not** be taken at the same time as antacids (see section 4.5).

A daily dose of up to **400 mg** of ofloxacin may be given **once daily**; in this case, it is preferable to administer the dose in the morning.

Above 400 mg/day, the dose **must** be divided into **two doses** (approximately 12 hours apart).

4.3 Contraindications

This medicinal product must **never** be used:

- in patients with hypersensitivity to ofloxacin, other quinolones, or any excipient listed in section 6.1,
- in epileptic patients,
- in patients with a history of tendinopathy related to quinolone therapy,
- in children or adolescents during the growth period* (see section 4.4),
- in pregnant or breastfeeding women* (see section 4.6).

*Based on animal studies, a risk of cartilage damage in growing individuals cannot be fully excluded.

4.4 Special warnings and precautions for use

Use of ofloxacin should be avoided in patients who have experienced serious adverse reactions with prior quinolone or fluoroquinolone therapy (see section 4.8). Treatment with ofloxacin should be initiated **only when no alternative treatment is available**, after a thorough benefit–risk assessment (see also section 4.3).

Risk of resistance

The prevalence of acquired resistance may vary by region and over time for certain species. It is useful to have local resistance data; microbiological diagnosis including pathogen isolation and susceptibility testing should be obtained, particularly for severe infections or cases with inadequate clinical response.

Infections due to streptococci and pneumococcus

Given the sensitivity levels of streptococci and pneumococcus to ofloxacin, ofloxacin is **not first-line therapy** for infections caused by these organisms.

Infections due to Escherichia coli

Resistance of *E. coli* to fluoroquinolones (a common urinary tract pathogen) varies across the EU. Prescribers must consider local *E. coli* resistance rates.

Methicillin-resistant *Staphylococcus aureus* (MRSA) often displays cross-resistance to fluoroquinolones, including ofloxacin. Therefore, ofloxacin is discouraged for suspected or confirmed MRSA infections unless susceptibility is proven and alternative recommended antibiotics are inappropriate.

Bone and joint infections

Combination therapy with other antibiotics should be considered.

Infections due to Neisseria gonorrhoeae

Due to the increasing resistance of *Neisseria gonorrhoeae*, ofloxacin must not be used as empirical treatment when a gonococcal infection is suspected (gonococcal urethral infection, pelvic inflammatory disease, or orchiepididymitis) unless the pathogen has been identified and confirmed as susceptible to ofloxacin.
If no clinical improvement is observed after 3 days of treatment, the choice of therapy must be reassessed.

Pelvic inflammatory disease

Ofloxacin must be used **only in combination** with anaerobic coverage.

Children and adolescents

Ofloxacin must not be used in children and adolescents until growth is complete due to joint toxicity: severe arthropathies affecting primarily large joints (see section 4.3). However, in exceptional cases, after microbiological documentation and careful assessment of the benefit–risk ratio, ofloxacin may be considered in children from the age of 6 years (this age limit is related to the pharmaceutical form, as tablet intake is not recommended in children under 6 years due to the risk of choking) and in adolescents, for the exceptional treatment of certain severe infections that have failed to respond to conventional therapy and for which bacteriological test results may justify the use of ofloxacin.

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 must be informed of the need to contact their doctor immediately before continuing treatment if reactions occur on the skin and/or mucous membranes.

Hypersensitivity

Hypersensitivity and allergic reactions have been reported with fluoroquinolones after the first administration. Anaphylactic and anaphylactoid reactions may be life-threatening, even after a single dose. In such cases, ofloxacin must be discontinued and appropriate treatment (e.g., management of anaphylactic shock) must be initiated.

Clostridium difficile-associated diarrhea

Diarrhoea, particularly when severe, persistent and/or bloody, occurring during treatment or up to 10 weeks after treatment with ofloxacin, may be a sign of *Clostridium difficile*-associated colitis (CDAD). The severity of CDAD can range from mild to life-threatening, with pseudomembranous colitis being the most severe form (see section 4.8).

Therefore, this diagnosis should be considered in patients who develop severe diarrhoea during or after treatment with ofloxacin. If CDAD is suspected or confirmed, ofloxacin must be discontinued immediately and appropriate treatment initiated without delay.

Medicines that inhibit peristalsis are contraindicated in patients who develop severe diarrhoea.

Patients predisposed to seizures

Quinolones may lower the epileptogenic threshold and trigger convulsive seizures. Ofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3).

As with other quinolones, ofloxacin must be used with great caution in patients predisposed to seizures.

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

If convulsive seizures occur, treatment with ofloxacin must be discontinued.

Serious, persistent, disabling, potentially irreversible adverse effects

Very rare cases of serious, persistent (lasting several months or years), disabling and potentially irreversible adverse reactions affecting different organs, sometimes involving multiple systems (musculoskeletal, nervous, psychiatric and sensory), have been reported in patients receiving quinolones and fluoroquinolones, regardless of age or pre-existing risk factors. Treatment with ofloxacin must be stopped immediately at the first signs or symptoms of a serious adverse reaction, and patients should be advised to contact their physician for medical advice.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (particularly, but not exclusively, involving the Achilles tendon), sometimes bilateral, may occur within the first 48 hours of treatment with quinolones and fluoroquinolones, and cases have been reported up to several months after stopping treatment. The risk of tendinitis and tendon rupture is increased in elderly patients, patients with renal impairment, patients who have received solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first signs of tendinitis (e.g., painful swelling, inflammation), treatment with ofloxacin must be discontinued and alternative therapy considered. The affected limb(s) should be treated appropriately

(e.g., immobilisation). Corticosteroids must not be used if signs of tendinopathy appear.
The risk of arthropathy should be monitored, particularly in children.
Specifically regarding children, if joint pain appears during treatment with ofloxacin, treatment must be stopped and the affected joint rested; specialist advice will be required.

Renal impairment
Because of predominantly renal elimination, dose adjustment is required (see section 4.2).

Patients with psychotic disorders
Psychotic reactions, including suicidal ideation and suicide attempts, have been reported in patients taking fluoroquinolones, including ofloxacin, sometimes even after a single dose (see section 4.8). In situations where a patient develops such reactions, treatment with ofloxacin must be discontinued immediately at the first signs or symptoms, and patients should be advised to contact their prescribing physician for medical guidance. An alternative antibacterial treatment without fluoroquinolones should be considered, and appropriate measures initiated.
Ofloxacin should be used with caution in patients who have or have had psychiatric disorders.

Hepatic impairment / severe liver disease
Ofloxacin should be used with caution in patients with impaired hepatic function, as treatment may cause liver injury. Cases of fulminant hepatitis that may lead to liver failure (including fatal outcomes) have been reported with ofloxacin. Patients must be advised to discontinue treatment and contact their physician if signs or symptoms of liver disease appear, such as anorexia, jaundice, dark-coloured urine, pruritus, or abdominal tenderness (see section 4.8).

Patients treated with vitamin K antagonists
Given the possible increase in coagulation test results (Prothrombin Time/INR) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in combination with vitamin K antagonists (e.g., warfarin), coagulation tests must be monitored when these medicines are administered concomitantly with ofloxacin (see section 4.5).

Myasthenia
Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia. During post-marketing surveillance, serious adverse events, including deaths and the need for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia.
Ofloxacin is not recommended in patients with a known history of myasthenia.

Photosensitivity prevention
Photosensitivity reactions have been reported with ofloxacin (see section 4.8). Patients should avoid unnecessary exposure to strong sunlight or artificial ultraviolet rays (sunlamps, tanning beds) during treatment and for 48 hours after stopping treatment to prevent photosensitization.

Secondary infections
As with other antibiotics, the use of ofloxacin, particularly for prolonged periods, may promote the growth of non-susceptible strains. Repeated assessment of the patient's condition is essential. If a secondary infection develops during treatment, appropriate measures must be taken.
Emergence of resistance or selection of resistant strains may occur, particularly during long-term treatment and/or in nosocomial infections, notably among staphylococci and *Pseudomonas*.

QT interval prolongation

Caution is advised when treating patients with fluoroquinolones, including ofloxacin, who have known risk factors for QT interval prolongation, such as:
• congenital long QT syndrome,
• concomitant treatment with medicinal products known to prolong the QT interval (e.g., class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics),
• uncorrected electrolyte imbalance (e.g., hypokalaemia, hypomagnesaemia),
• cardiac conditions (such as heart failure, myocardial infarction, or bradycardia).

Elderly patients and women may be more sensitive to treatments that prolong the QTc interval. Therefore, caution is recommended when treating these populations with fluoroquinolones, including ofloxacin (see sections 4.2, 4.5, 4.8 and 4.9).

Aortic aneurysm, aortic dissection, and cardiac valve regurgitation/insufficiency
Epidemiological studies have reported an increased risk of aortic aneurysm and aortic dissection, particularly in elderly individuals, as well as aortic and mitral valve regurgitation, after the use of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ruptures), and cases of cardiac valve regurgitation/insufficiency have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should be used only after careful benefit-risk assessment and after considering alternative therapeutic options in patients with a family history of aneurysmal disease or congenital valvulopathy, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or cardiac valvular disease, or who present other risk factors or conditions predisposing:
• to both aortic aneurysm, aortic dissection, and cardiac valve regurgitation/insufficiency (e.g., connective tissue disorders such as Marfan syndrome or Ehlers–Danlos syndrome, Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis), or
• to aortic aneurysm and dissection (e.g., vascular disorders such as Takayasu arteritis or giant-cell arteritis [Horton's disease], known atherosclerosis, or Sjögren's syndrome), or
• to cardiac valve regurgitation/insufficiency (e.g., infective endocarditis).

The risk of aortic aneurysm and dissection, as well as of aortic valve rupture, may also be increased in patients receiving systemic corticosteroids concurrently.

In the event of sudden abdominal, chest, or back pain, patients should be advised to immediately seek emergency medical care.
Patients should also be advised to seek immediate medical attention in cases of acute dyspnoea, onset of palpitations, or development of abdominal or lower limb oedema.

Dysglycaemia

As with all quinolones, disturbances in blood glucose levels — including both hypoglycaemia and hyperglycaemia — have been reported, occurring more frequently in elderly patients, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (such as glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, close monitoring of blood glucose is recommended (see section 4.8).
Treatment with OFLOCET must be discontinued immediately if a patient reports disturbances in blood glucose, and an alternative antibacterial treatment without fluoroquinolones should be considered.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy, presenting as paraesthesia, hypoesthesia, dysesthesia or muscle weakness, have been reported in patients treated with quinolones and fluoroquinolones. To prevent potential progression to an irreversible condition, patients treated with ofloxacin should be advised to contact their doctor before continuing treatment if symptoms of neuropathy such as pain, burning sensations, tingling, numbness or muscle weakness appear (see section 4.8).

Visual disorders

If visual disturbances or any other ocular manifestations occur, an ophthalmologist must be consulted immediately (see sections 4.7 and 4.8).

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate dehydrogenase enzyme deficiency may be predisposed to haemolytic reactions if treated with quinolones. Therefore, if ofloxacin must be used in these patients, monitoring for signs of haemolysis is recommended.

Patients with rare hereditary disorders

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interference with laboratory tests

Testing for opiates or porphyrins in urine may yield false-positive results during treatment with ofloxacin. Confirmation using more specific detection methods may be necessary.
The activity of ofloxacin against *Mycobacterium tuberculosis* may suppress the detection of *M. tuberculosis* (BK), particularly in pulmonary or osteoarticular tuberculosis.

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

Combinations requiring precautions for use

Antacids, sucralfate, metal cations

Antacids containing aluminium (including sucralfate) and magnesium hydroxide, aluminium phosphate, zinc, or iron reduce the absorption of ofloxacin tablets.
Ofloxacin should be administered approximately **2 hours apart** from antacids.

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

No pharmacokinetic interaction between ofloxacin and theophylline was found in a clinical study. However, a marked lowering of the seizure threshold may occur when quinolones are given simultaneously with theophylline, NSAIDs, or other medicines that lower the seizure threshold.

Medicines known to prolong the QT interval

As with other fluoroquinolones, ofloxacin 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 (VKAs)

Increased coagulation tests (PT/INR) and/or bleeding, potentially severe, have been reported in patients treated with ofloxacin combined with VKAs (e.g., warfarin).
More frequent INR monitoring is required.
Dose adjustment of the VKA may be necessary during and after treatment with the fluoroquinolone (see section 4.4).

Glibenclamide

Ofloxacin may cause a slight increase in serum glibenclamide concentrations when given concurrently. Patients receiving both medications should therefore be closely monitored.

Probenecid, cimetidine, furosemide or methotrexate

Probenecid lowers total clearance of ofloxacin by 24% and increases AUC by 16%, likely through competition or inhibition of active renal tubular secretion.

Caution is recommended when ofloxacin is administered with medicines affecting renal tubular secretion (especially probenecid, cimetidine, furosemide or methotrexate), particularly at high doses.

Strontium

Reduced gastrointestinal absorption of strontium.

Strontium should be taken at a distance from fluoroquinolones (more than 2 hours, if possible).

Combinations to be taken into account

Glucocorticoids (except replacement hydrocortisone)

Possible increased risk of tendinopathy, including rare tendon rupture, especially in patients receiving prolonged corticosteroid therapy.

Mycophenolate mofetil

Reduction of mycophenolic acid levels by about one-third, with a potential risk of decreased efficacy.

Specific issue: INR imbalance

Numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics. Marked infectious or inflammatory conditions, age, and general patient status appear to be risk factors.

In such cases, it can be difficult to distinguish the contribution of the infection itself from that of the antibiotic in causing INR imbalance.

However, certain antibiotic classes are more frequently implicated: fluoroquinolones, macrolides, tetracyclines, cotrimoxazole, and certain cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on limited human data, the use of fluoroquinolones during the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse pregnancy outcomes. Animal studies have shown joint cartilage damage in immature animals, but no teratogenic effects. Therefore, **ofloxacin must not be used during pregnancy** (see section 4.3).

Joint disorders have been described in children treated with quinolones, but to date, no cases of arthropathy secondary to in-utero exposure have been reported.

Breast-feeding

Ofloxacin is excreted in breast milk in small amounts. Because of the risk of arthropathy and other serious toxicities in the breastfed infant, **breast-feeding must be discontinued during treatment** with ofloxacin (see section 4.3).

4.7 Effects on ability to drive and use machines

Reactions (e.g., dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore pose a risk in situations where these abilities are of particular importance (e.g., driving a vehicle or operating machinery).

4.8 Undesirable effects

The information below is based on data from clinical trials and extensive post-marketing experience.

System organ class	Frequent (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Frequency not known (cannot be estimated from available data)
Infections and infestations			Fungal infections, Bacterial resistance		
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure	
Immune system disorders			Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*	Anaphylactic shock*, Anaphylactoid shock*	
Metabolism and nutrition disorders			Anorexia, Hypoglycaemic coma (see section 4.4)		Hypoglycaemia in diabetic patients treated with hypoglycaemic agents*, Hyperglycaemia
Psychiatric disorders[1]		Agitation, Sleep disorders, Insomnia	Psychotic disorders (e.g., hallucination), Anxiety, Confusional state, Nightmares, Depression, Delirium, Memory disorders		Psychotic disorders and depression endangering the patient, including suicidal ideation or suicide attempts (see section 4.4), Nervousness
Nervous system disorders[1]		Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy*, Peripheral sensorimotor neuropathy*, Convulsions,	Tremor, Dyskinesia, Ageusia, Syncope, Benign intracranial hypertension (pseudotumor cerebri)

				Extrapyramidal symptoms or other coordination disorders	
Eye disorders[1]		Eye irritation	Visual disturbances		Uveitis
Ear and labyrinth disorders[1]		Vertigo		Tinnitus, Hearing loss	Hearing difficulties
Cardiac disorders **			Tachycardia		Ventricular arrhythmias, Torsade de pointes (events mostly observed in patients with QT prolongation risk factors), QT interval prolongation confirmed by ECG (see sections 4.4 and 4.9)
Vascular disorders **			Hypotension		
Respiratory, thoracic and mediastinal disorders		Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonia, Severe dyspnoea
Gastrointestinal disorders		Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis (sometimes haemorrhagic)	Pseudomembranous colitis*	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders			Increased liver enzymes (ALT, AST, LDH, gamma-GT and/or alkaline phosphatases), Increased blood bilirubin	Cholestatic jaundice	Hepatitis, potentially severe. Cases of severe liver injury, including acute liver failure (sometimes fatal), have been reported with ofloxacin, mainly in

					patients with underlying liver disease.*
Skin and subcutaneous tissue disorders		Pruritus, Rash	Urticaria, Flushing, Hyperhidrosis, Pustular rash	Erythema multiforme, Bullous epidermal necrolysis, Photosensitivity reaction*, Drug eruption, Vascular purpura, Vasculitis (which may exceptionally lead to skin necrosis)	Stevens–Johnson syndrome, Acute generalised exanthematous pustulosis, Drug eruption, Lyell's syndrome, Stomatitis, Exfoliative dermatitis
Musculoskeletal and connective tissue disorders[1] and bone disorders			Tendinitis	Arthralgia, Myalgia, Tendon rupture (e.g., Achilles tendon), which may occur within 48 hours of treatment onset and may be bilateral	Rhabdomyolysis and/or myopathy, Muscle weakness, Muscle tear, Muscle rupture, Ligament rupture, Arthritis, Possible worsening of myasthenia*
Renal and urinary disorders			Increased serum creatinine	Acute renal failure	Acute interstitial nephritis
Congenital, familial and genetic disorders					Porphyria attacks in patients with porphyria
General disorders and administration site conditions[1]					

*see section 4.4.

** Cases of aortic aneurysm and aortic dissection, sometimes complicated by rupture (including fatal ruptures), and cases of cardiac valve regurgitation/insufficiency have been reported in patients receiving fluoroquinolones (see section 4.4).

[1] Very rare cases of serious, persistent (lasting several months or years), disabling and potentially irreversible adverse reactions affecting various sensory organ systems—sometimes involving multiple systems—have been reported in association with quinolones and fluoroquinolones. These include effects such as tendinitis, tendon rupture, arthralgia, pain in the extremities, gait disturbances, neuropathies with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and disturbances of hearing, vision, taste, and smell, sometimes occurring independently of pre-existing risk factors (see section 4.4).

Paediatric population

In children: arthropathies (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after a medicinal product has been authorised is important. It enables continuous monitoring of the benefit–risk balance of the medicine. Healthcare professionals should report any suspected adverse reactions via the national reporting system:
French National Agency for Medicines and Health Products Safety (ANSM) and the network of Regional Pharmacovigilance Centres – Website: https://signalement.social-sante.gouv.fr/.

4.9 Overdose

Analysis of overdose cases in humans shows that most often, the patients are elderly, and in one-third of cases, the overdose is linked to failure to adjust the dose according to renal function.

The most frequent signs observed following ofloxacin overdose are central nervous system symptoms such as confusion, dizziness, impaired consciousness, and convulsive seizures; QT interval prolongation; and gastrointestinal reactions such as nausea and gastric mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been reported since the product's marketing.

In case of overdose, symptomatic treatment must be initiated.
Antacids may be used to protect the gastric mucosa.

Knowledge of renal function (creatininaemia) is useful to assess the possibilities of drug elimination. It is recommended to avoid excessive musculoskeletal strain in the days following the overdose and gradually resume normal physical activity thereafter.

A fraction of ofloxacin can be eliminated from the body by haemodialysis. Peritoneal dialysis and continuous ambulatory peritoneal dialysis are ineffective in eliminating ofloxacin. No specific antidote exists.

Electrocardiographic (ECG) monitoring must be performed due to the risk of QT interval prolongation. Neurological clinical monitoring must also be carried out.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: fluoroquinolone, ATC code: J01MA01.
Ofloxacin is a synthetic antibiotic belonging to the quinolone family, specifically the fluoroquinolone group.

Mechanism of action

Its activity is strongly bactericidal through inhibition of bacterial DNA gyrase, preventing the synthesis of bacterial chromosomal DNA.

Breakpoints

Breakpoints distinguish susceptible strains from those with intermediate sensitivity and from resistant strains.

The minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are presented below.

EUCAST breakpoints for ofloxacin (2012-01-01, v.2.0)

Organisms	Susceptible (S) (mg/L)	Resistant (R) (mg/L)
Enterobacteriaceae	≤ 0.5	> 1
Staphylococcus spp.	≤ 1	> 1
Streptococcus pneumoniae	≤ 0.12	> 4
Haemophilus influenzae	≤ 0.5	> 0.5
Moraxella catarrhalis	≤ 0.5	> 0.5
Neisseria gonorrhoeae	≤ 0.12	> 0.25
Non-species-related breakpoints*	≤ 0.5	> 1

* Non-species-related breakpoints were determined mainly on the basis of PK/PD data and are independent of MIC distributions for specific species. They apply only to species for which no species-specific breakpoint has been defined and not to species for which susceptibility testing is not recommended.

Fluoroquinolones have **concentration-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 the ratio between the **maximum serum concentration (Cmax)** and the MIC, is predictive of clinical success.

The prevalence of resistance may vary depending on **geographical location** and **time period** for certain species. It is useful to have information on local resistance patterns, especially for the treatment of severe infections. When necessary, expert advice should be sought, particularly when the usefulness of the medicinal product for certain infections may be questionable due to local resistance prevalence.

Resistance to ofloxacin is acquired **stepwise** through mutations in the target sites of the two type II topoisomerases: **DNA gyrase** and **topoisomerase IV**. Other resistance mechanisms, such as **membrane-based mechanisms** (common in *Pseudomonas aeruginosa*) and **efflux mechanisms**, may also affect susceptibility to ofloxacin.

Classification of species according to susceptibility to ofloxacin

CLASSIFICATION

SPECIES USUALLY SUSCEPTIBLE

*including species with intermediate susceptibility

- *Bacillus anthracis*
- *Bordetella pertussis*
- *Campylobacter*
- *Chlamydia*
- *Chlamydophila pneumoniae*
- *Corynebacteria*
- *Enterobacter*
- *Haemophilus influenzae*
- *Legionella pneumophila*
- *Moraxella catarrhalis*
- *Morganella morganii*
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- *Proteus vulgaris*
- *Salmonella*
- *Shigella*
- *Streptococci*
- *Ureaplasma urealyticum*
- *Yersinia*

SPECIES WITH VARIABLE SUSCEPTIBILITY

(Possibility of acquired resistance)

- *Citrobacter freundii*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Neisseria gonorrhoeae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Serratia*
- Coagulase-negative *Staphylococci*
- *Staphylococcus aureus* (methicillin-sensitive)
- *Streptococcus pneumoniae*

SPECIES NATURALLY RESISTANT

- *Acinetobacter baumannii*
- *Bacteroides spp.*
- *Clostridium difficile*
- *Enterococci*
- *Listeria monocytogenes*
- *Methicillin-resistant Staphylococci*
- *Nocardia*

5.2 Pharmacokinetic properties

In subjects with normal renal function

Absorption

After oral administration of ofloxacin in fasting subjects, absorption is extensive and rapid, with peak serum levels occurring after approximately one hour on average.

Distribution

The maximum serum concentration after a single 200 mg dose is between **2.5 and 3 µg/mL** on average.
The serum elimination half-life is **6 to 7 hours**. Elimination is linear.
The apparent volume of distribution is **120 litres**.

After repeated administration, serum concentrations are not significantly increased (accumulation factor approximately **1.5**).

Ofloxacin concentrations in the urine and at the site of urinary infection exceed serum concentrations by **5- to 100-fold**.

Plasma protein binding is low, about **10%**.
The apparent volume of distribution is high: approximately **1.5 L/kg**.

Ofloxacin shows strong tissue affinity, with tissue levels exceeding serum concentrations, particularly in the following sites: pulmonary parenchyma, salivary glands, oropharyngeal mucosa, skin, muscle, bone, prostate, lymph nodes, gynaecological tissues, as well as in saliva and bronchial mucus.

Biotransformation

Biotransformation is very limited (less than **5%** metabolites recovered in urine).

Elimination

Excretion is mainly renal (**80%** of the administered dose is recovered unchanged in the urine).

In elderly subjects

After a single 200 mg or 400 mg dose, the elimination half-life is prolonged, with no major change in maximum serum concentration.

In subjects with renal impairment

The elimination half-life is prolonged, and both total and renal clearance are reduced proportionally to the degree of renal impairment.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Maize starch
- Carmellose
- Hydroxypropylcellulose
- Lactose monohydrate
- Magnesium stearate
- Hypromellose

- Titanium dioxide
- Macrogol 8000
- Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product should be stored at room temperature.

6.5 Nature and contents of container
Blister packs of **10 and 50 tablets** (PVC/Aluminium).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER

TAMRISA ACCESS

22, rue de la Fédération

75015 Paris

France

8. DATE OF REVISION OF THE TEXT

Updated on: **06/03/2025**

9. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.