Core Safety Profile

**Active substance:** Ofloxacin

**Pharmaceutical form(s)/strength:** Tablets, 200mg

**P-RMS:** SE/H/PSUR/0041/001

**Date of FAR:** 25.03.2010
SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF MEDICINAL PRODUCT**

Ofloxacin (INN).

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

*applies to the tablets:*

Active ingredient:
Each film-coated tablet contains 100 mg, 200 mg or 400 mg of ofloxacin respectively.

Excipients:
Tablet core
100 mg and 200 mg tablets: maize starch; carboxypropylcellulose; hydroxypropylcellulose; lactose; magnesium stearate.
400 mg tablets: lactose; maize starch glycolate; hyprolose 7.5 mPa; carmellose sodium 1000 mPa; magnesium stearate.

Tablet coating
100 mg and 200 mg tablets: methylhydroxypropylcellulose 6 CPS; titanium dioxide; polyethylene glycol 6000; talc.
400 mg tablets: hypromellose 5 mPa; hypromellose 3 mPa; macrogol 6000; polysorbate 80; titanium dioxide; and yellow ferric oxide.

*applies to the solution for infusion:*

Active ingredient:
Each bottle contains 100 mg, 200 mg or 400 mg of ofloxacin, equivalent to 110 mg, 220 mg or 440 mg ofloxacin hydrochloride respectively.

Excipients:
Sodium chloride; hydrochloric acid qs pH 4.5; water for injection:
(2 % concentration = 2mg/ml) qs 50 ml/100 ml/200 ml for 100 mg, 200 mg and 400 mg respectively.
(5 % concentration = 5mg/ml) qs 40 ml for 200 mg.

3. **PHARMACEUTICAL FORM**

Film-coated scored tablets.

Solution for intravenous infusion.

4. **CLINICAL PARTICULARS**

4.1  **Therapeutic Indications**

The following indications are restricted to adults.

Bacterial infections due to ofloxacin-susceptible micro-organisms as follows:

- Renal, urinary tract, prostatic, urethral gonococcal infections
- Skin and soft-tissue infections
- Bone and joint infections
- Gynaecological infections,
- Abdominal and biliary tract infections
- Ear, nose, throat infections (except acute tonsillitis*)
- Respiratory tract infections (except if pneumococcal infection is suspected or diagnosed*)
- Prevention of infections due to ofloxacin susceptible pathogens (prophylaxis of infections, also by selective decontamination of the intestine) in patients with a significant reduction in resistance to infections (e.g., in neutropenic states)
- Septicaemia (injectable solution only)

* Since some strains are only partially sensitive to ofloxacin, it should not be used as first choice treatment of community acquired pneumonia (because of Streptococcus pneumoniae) and acute tonsillitis (because of β-haemolytic Streptococci).

4.2 **Posology and Method of Administration**

Dosage and route of administration depend on the type and severity of the infection, and are generally based on the following guidelines.

**Dosing in adults with normal renal function** (e.g. creatinine clearance > 50 ml/min)

Dose regimens according to authorized indications are given in the following table:

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>UNIT DOSE (oral or I.V.) mg</th>
<th>NUMBER of doses / 24 h</th>
<th>INTERVAL between doses* h</th>
<th>DAILY DOSE** mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections with susceptible organisms</td>
<td>200</td>
<td>2</td>
<td>12</td>
<td>400</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis***</td>
<td>400</td>
<td>1</td>
<td>24</td>
<td>400</td>
</tr>
</tbody>
</table>

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

** The dose may be increased to 600 mg (or even to 800 mg for the tablets) for treatment of severe infections or in overweight patients.

*** Registered in France and UK only.

**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)

**Posology in patients with renal insufficiency**

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

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE</th>
<th>UNIT DOSE mg*</th>
<th>NUMBER / 24 h</th>
<th>INTERVALS h</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 - 20 ml/min</td>
<td>100 – 200</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>&lt; 20 ml/min** or haemodialysis or peritoneal dialysis</td>
<td>100 or 200</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

* 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:

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

or

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

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

Posology in hepatic insufficiency (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.

Type and duration of treatment

Applies to all dosage forms:

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.

Applies to the tablets:

Tablets are to be swallowed with sufficient amount of liquids. They may be taken on an empty stomach or with meals. Concomitant administration with antacids should be avoided. (See 4.5: Interactions)

Applies to the solution for infusion:

Ofloxacin solution is only intended for SLOW intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 200mg of ofloxacin solution. This is of particular importance when ofloxacin is administered concomitantly with drugs that can lead to a reduction in blood pressure or with barbiturate-containing anaesthetics.

It is possible to switch from an initial intravenous application to the oral route at the same dosage after a few days, according to the condition of the patient.

Duration of treatment

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ofloxacin should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.
4.3 Contraindications

Ofloxacin must not be used

- in patients hypersensitive to ofloxacin, other quinolones, or any of the excipients
- in patients with epilepsy
- 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.

4.4 Special warnings and special precautions for use

Comment: The order of warnings should be given according to severity in line with the SPC guideline.

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

- 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.

- *Clostridium difficile*-associated disease

Diarrhea, particularly if severe, persistent and/or bloody, during or up to 10 weeks after treatment with ofloxacin, may be symptomatic of pseudo-membranous colitis. 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). Products inhibiting the peristalsis are contraindicated in this clinical situation

- Patients predisposed to seizures

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: Interactions)

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

- Tendonitis

Tendonitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. Elderly patients are more prone to tendonitis. The risk of tendon rupture may be...
increased by co-administration of corticosteroids. If tendonitis is suspected, treatment with ofloxacin must be discontinued immediately.

Appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

- 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: Dosage and Administration).

- 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. In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted.

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

- Patients with impaired liver function/serious liver damage

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 ofloxacin. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen. (See section 4.8: Undesirable effects)

- 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

Ofloxacin should be used with caution in patients with a history of myasthenia gravis.

- Prevention of photosensitisation

Because of the risk of photosensitisation, exposure to strong sunlight and UV radiation should be avoided during treatment with ofloxacin.

- Secondary infection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If secondary infection occurs during therapy, appropriate measures should be taken.

- 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
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- congenital long QT syndrome
- 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 section 4.2 Elderly and section 4.5, section 4.8 and section 4.9).

- Hypoglycemia

As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended. (See section 4.8)

- Peripheral neuropathy

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

- Patients with rare hereditary disorders

Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

applies to the tablets:

- Antacids, Sucrulate, 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.

applies to all dosage forms:

- Theophylline, fenbufen or similar non-steroidal antiinflammatory drugs

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

Interaction 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.

Vitamin K antagonists

Coagulation tests should be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

Glibenclamide

Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; it is therefore recommended that patients treated concomitantly with ofloxacin and glibenclamide be monitored particularly closely.

Probenecid, cimetidine, furosemide, or methotrexate.

Particularly in case of high dose therapy, mutual impairment of excretion and an increase in serum levels must be considered when quinolones are administered together with other drugs that also undergo renal tubular secretion (such as probenecid, cimetidine, furosemide or methotrexate).

4.6 Pregnancy and Lactation

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: Contraindications)

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: Contraindications)

4.7 Effects on Ability to Drive and to Use Machines

Some adverse reactions (e.g. dizziness/vertigo, drowsiness, visual disturbances) 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).

4.8 Undesirable Effects

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

<p>| System organ class | Common (≥1/100 to &lt;1/10) | Uncommon (≥1/1,000 to &lt;1/100) | Rare (≥1/10,000 to &lt;1/1,000) | Very rare (&lt;1/10,000) | Not known (cannot be estimated from available data) |</p>
<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common (≥1/10 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Fungal infection, Pathogen resistance</td>
<td></td>
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</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td>Anaemia Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia</td>
<td>Agranulocytosis Bone marrow failure</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*</td>
<td>Anaphylactic shock*, Anaphylactoid shock*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition disorders</td>
<td></td>
<td>Anorexia</td>
<td></td>
<td>Hypoglycaemia in diabetics treated with hypoglycaemic agents</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation, Sleep disorder, Insomnia</td>
<td>Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression</td>
<td></td>
<td>Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt’</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Headache</td>
<td>Somnolence, Paraesthesia, Dysgeusia, Parosmia</td>
<td>Peripheral sensory neuropathy* Peripheral sensory motor neuropathy* Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye irritation</td>
<td>Visual disturbance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td></td>
<td>Tinnitus, Hearing loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System organ class</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td>Very rare (&lt; 1/10,000)</td>
<td>Not known (cannot be estimated from available data)</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Tachycardia</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>applies only to the solution for infusion: Phlebitis</td>
<td></td>
<td>Hypotension</td>
<td></td>
<td>applies only to the solution for infusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>During infusion of ofloxacin, tachycardia and hypotension may occur. Such a decrease in blood pressure may, in very rare cases, be severe.</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough, Nasopharyngitis</td>
<td></td>
<td>Dyspnoea, Bronchospasm</td>
<td></td>
<td>Allergic pneumonitis, Severe dyspnoea</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Abdominal pain, Diarrhoea, Nausea, Vomiting</td>
<td></td>
<td>Enterocolitis, sometimes haemorrhagic</td>
<td></td>
<td>Pseudo-membranous colitis*</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td>Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) Blood bilirubin increased</td>
<td>Jaundice cholestatic</td>
<td>Hepatitis, which may be severe*</td>
</tr>
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<td></td>
</tr>
<tr>
<td>System organ class</td>
<td>Common (≥1/100 to &lt;1/10)</td>
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<td>Very rare (&lt; 1/10,000)</td>
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</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus, Rash</td>
<td>Urticaria, Hot flushes, Hyperhidrosis Pustular rash</td>
<td>Erythema multiforme, Toxic epidermal necrolysis, Photo-sensitivity reaction*, Drug eruption Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis</td>
<td>Stevens-Johnson syndrome; Acute generalized exanthemous pustulosis; drug rash</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective tissue disorders</td>
<td>Tendonitis</td>
<td>Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral.</td>
<td>Rhabdomyolysis and/or Myopathy, Muscular weakness Muscle tear, muscle rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary disorders</td>
<td>Serum creatinine increased</td>
<td>Acute renal failure</td>
<td>Acute interstitial nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital and familial/genetic disorders</td>
<td></td>
<td></td>
<td>Attacks of porphyria in patients with porphyria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>applies only to the solution for infusion: Infusion site reaction (pain, reddening)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* see section 4.4

### 4.9 Overdosage

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

In the event of overdose **symptomatic treatment should be implemented, ECG monitoring should be undertaken, because of the the possibility of QT interval prolongation.**