SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ofloxacin Teva 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated Tablet contains 400 mg of Ofloxacin.

Excipient(s) with known effect
This product contains lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets
White, round Film-coated Tablets, 11mm diameter, scored on both sides. One side of the tablet is debossed “FXN” on one side of the breakline and “200” on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ofloxacin is indicated for the treatment of the following infections when caused by sensitive organisms (see section 5.1):
- upper and lower urinary tract infections;
- lower respiratory tract infections such as acute exacerbation of chronic bronchitis or pneumonia if caused by Gram-negative bacteria. Ofloxacin is not the treatment of choice for community acquired pneumonia;
- uncomplicated urethral and cervical gonorrhoea;
- non-gonococcal urethritis and cervicitis.

Consideration should be given to official guidance on the appropriate use of anti-bacterial agents.
4.2 Posology and method of administration

Posology

*General dosage recommendations:*
The dose of ofloxacin should be determined by the type and severity of the infection.

The dosage range for adults is 200 mg to 800 mg daily. Up to 400 mg may be given
as a single dose, preferably in the morning. In individual cases it may be necessary to
increase the dose to 600 mg (or even to a maximum total dose of 800 mg daily) for
treatment of severe infections or in overweight patients. Daily doses of more then 400
mg must be divided into two separate doses and be given at approximately equal
intervals..

<table>
<thead>
<tr>
<th>Indications</th>
<th>Single and daily doses</th>
<th>Usual duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated lower urinary tract infections</td>
<td>200–400 mg daily</td>
<td>3 days</td>
</tr>
<tr>
<td>Complicated infections of the kidneys and urinary tract</td>
<td>400 mg daily, increasing if necessary, to 400 mg twice a day</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>400 mg daily, increasing, if necessary, to 400 mg twice a day</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Uncomplicated gonorrhoea</td>
<td>400 mg</td>
<td>Single dose</td>
</tr>
<tr>
<td>Non-gonococcal urethritis and cervicitis</td>
<td>400 mg daily</td>
<td>7-10 days</td>
</tr>
</tbody>
</table>

*Renal impairment:*
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</th>
<th>Number /24 hours</th>
<th>Intervals hours</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**</td>
<td>100</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>or haemodialysis</td>
<td>or 200</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>or peritoneal dialysis</td>
<td></td>
<td></td>
<td></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:
Hepatic impairment (e.g. cirrhosis with ascites)
It is recommended that a maximum daily dose of 400 mg of ofloxacin be not exceeded, because of possible reduction of excretion.

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

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

Type and duration of treatment
A daily dose of up to 400mg ofloxacin may be given as a single dose. In this case, it is preferable to administer ofloxacin in the morning.
Daily doses of more than 400mg must be divided into two separate doses and be given at approximately equal intervals.

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

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

Treatment should not exceed 2 months duration.

Method of administration:
Ofloxacin 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 section 4.5).

4.3 Contraindications

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

or

\[
\text{Women: ClCr (ml/min) = 0.85 x (above value)}
\]
Ofloxacin must not be used

- in patients with known hypersensitivity to ofloxacin, to other 4-quinolone antibacterials or to any of the excipients listed in section 6.1..

- in patients with a history of tendon disorders related to fluoroquinolone administration.

- in patients with epilepsy.

- 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 precautions for use

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

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

Resistance to fluoroquinolones of E. coli – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in E. coli to fluoroquinolones.

Severe bullous reactions Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with ofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

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

Clostridium difficile-associated disease
Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin (including several weeks after treatment), may be symptomatic of pseudo-membranous colitis (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop
serious diarrhoea during or after treatment with ofloxacin. If pseudo-membranous colitis is suspected, ofloxacin must be stopped immediately. Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products inhibiting the 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 (see section 4.3) and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

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

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

Tendonitis

Tendonitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. Tendonitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with ofloxacin and have been reported up to several months after discontinuation of. The risk of tendonitis and tendon rupture is increased in patients aged over 60 years and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance (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. If tendonitis is suspected, treatment with ofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon (see sections 4.3 and 4.8).

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

Patients with history of psychotic disorder
Psychotic reactions have been reported in patients receiving fluoroquinolones including ofloxacin. In some cases these have progressed to suicidal thoughts or self-endangering behavior including suicide attempt, sometimes after a single dose of ofloxacin (see section 4.8). In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted. Ofloxacin should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

Patients with hepatic impairment
Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritis or tender abdomen (see section 4.8).
Patients treated with vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

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

Prevention of photosensitisation
Photosensitisation has been reported with ofloxacin (see section 4.8). It is recommended that patients should 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.

Super 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:

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

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

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic 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)

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. 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 eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Interference with laboratory tests

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

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 Interaction with other medicinal products and other forms of interaction

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

Theophylline, fenbufen or similar non-steroidal 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).

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, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4).

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursing infant, breast feeding should be discontinued during treatment with ofloxacin (see section 4.3).

4.7 Effects on ability to drive and use machines

Some adverse reactions (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the 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.
<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common (≥1/100 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>
<td>Anaemia, Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia</td>
<td>Agranulocytosis, Bone marrow failure</td>
<td>Bone marrow failure may lead to pancytopenia</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*</td>
<td></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>Hypoglycaemia in diabetics treated with hypoglycaemic agents (see section 4.4)</td>
<td>Hypoglycaemia, Hypoglycaemic coma</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>Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)</td>
<td>Nervousness</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Headache</td>
<td>Somnolence, Parasthesia, Dysgeusia, Parosmia</td>
<td>Peripheral sensory neuropathy*, Peripheral sensory motor neuropathy*, Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination</td>
<td>Tremor, Dyskinesia, Ageusia, Syncope</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>
</tr>
<tr>
<td>--------------------</td>
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<td>-----------------------------</td>
<td>----------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye irritation</td>
<td>Visual disturbance</td>
<td>Tinnitus, Hearing loss</td>
<td>Hearing impaired</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Tachycardia</td>
<td></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></td>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough, Nasopharyngitis</td>
<td>Dyspnoea, Bronchospasm</td>
<td></td>
<td></td>
<td>Allergic pneumonitis, Severe dyspnoea</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Abdominal pain, Diarrhoea, Nausea, Vomiting</td>
<td>Enterocolitis, sometimes haemorrhagic</td>
<td>Pseudo-membranous colitis* Jaundice cholestatic</td>
<td></td>
<td>Dyspepsia Flatulence Constipation Pancreatitis</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) Blood bilirubin increased</td>
<td></td>
<td></td>
<td>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).</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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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus, Rash 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 Stomatitis; Exfoliative dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective tissue disorders</td>
<td>Tendonitis 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 Ligament rupture Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary disorders</td>
<td>Serum creatinine increased Acute renal failure</td>
<td>Acute interstitial nephritis</td>
<td>Attacks of porphyria in patients with porphyria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital and familial/genetic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthenia Pyrexia Pain (including pain in back, chest, and extremities)</td>
</tr>
</tbody>
</table>

* postmarketing experience

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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.
4.9 Overdose

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: fluoroquinolones
ATC code: J01 MA 01

Mechanism of action
Ofloxacin inhibits bacterial DNA replication in a range of gram-positive and gram-negative pathogenic bacteria by inhibiting bacterial topoisomerases, particularly DNA gyrase and topoisomerase IV.

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

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

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

According to DIN 58 940, the following limits apply for ofloxacin:
S ≤ 1 mg/L, I =2 mg/L, R ≥ 4 mg/L.
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ofloxacin or not.
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is question

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
<th>European range of acquired bacterial resistance to ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive microorganisms</strong></td>
<td></td>
</tr>
<tr>
<td>Providentia*</td>
<td>17.1%</td>
</tr>
<tr>
<td>S. aureus – methicillin-sensitive</td>
<td>0.3-12.6%</td>
</tr>
<tr>
<td>S. pneumoniae*</td>
<td>70%</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>2-5%</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative microorganisms</strong></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>0.3-7.3%</td>
</tr>
<tr>
<td>Citrobacter spp</td>
<td>3-15%</td>
</tr>
<tr>
<td>E. Faecalis*</td>
<td></td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>2-13%</td>
</tr>
<tr>
<td>E.coli</td>
<td>1-8%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>1%</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>1-10%</td>
</tr>
<tr>
<td>Morazella spp</td>
<td>0-0.2%</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>25%</td>
</tr>
<tr>
<td>P. aeruginosa*</td>
<td>20-30%</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>1-15%</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2-2.4%</td>
</tr>
<tr>
<td>Serratia spp*</td>
<td>20-40%</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia*</td>
<td>5.1-11%</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Chlamydia spp</td>
<td></td>
</tr>
<tr>
<td>L. pneumophila</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma spp*</td>
<td>0-5.3%</td>
</tr>
<tr>
<td>Ureaplasma spp*</td>
<td>0-2.1%</td>
</tr>
<tr>
<td><strong>Inherently resistant organisms</strong></td>
<td></td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td></td>
</tr>
<tr>
<td>S. aureus – methicillin-resistant</td>
<td>69.2-85.7%</td>
</tr>
<tr>
<td>T. pallidum</td>
<td></td>
</tr>
</tbody>
</table>

*These species show natural intermediate susceptibility ( in the absence of acquired mechanisms of resistance) to Ofloxacin.

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

5.2 Pharmacokinetic properties

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

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

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

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

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

5.3 Preclinical safety data

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep container in the outer carton to protect the tablets from light. Store in the original package.
6.5 Nature and contents of container

Transparent PVC/PVdC-aluminium blisters / white opaque PVC/PVdC-aluminium blisters
Blister packs of 5, 10, 20 and 50 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER
UK
Teva Pharma B.V.
Swensweg 5,
2031 GA Haarlem,
The Netherlands

8 MARKETING AUTHORISATION NUMBER
PL 14776/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/07/2006

10 DATE OF REVISION OF THE TEXT