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This information is intended for use by health professionals

1. Name of the medicinal product

Ofloxacin IV Infusion Solution.

2. Qualitative and quantitative composition

Ofloxacin, 2 mg/ml.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for Infusion.

4. Clinical particulars

4.1 Therapeutic indications

Ofloxacin is indicated in adults for the treatment of the following bacterial infections (see sections 4.4 and 5.1):

- Acute Pyelonephritis and complicated urinary tract infections

- Bacterial prostatitis, epididymo-orchitis

- Pelvic inflammatory disease, in combination with other antibacterial agents

- Urosepsis

For the below-mentioned infections ofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections:

- Complicated skin and soft-tissue infections

- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis

- Community acquired pneumonia

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

4.2 Posology and method of administration

General dosage recommendations: The dose of ofloxacin is determined by the type and severity of the infection. A daily dose of up to 400 mg ofloxacin may be given as a single dose. In this case, it is preferable to administer ofloxacin in the morning.

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

Adults: The usual intravenous dosages in adults are:

Acute exacerbation of chronic bronchitis, community acquired pneumonia: 200 mg twice daily.

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

The dose may be increased to 400 mg twice daily in severe or complicated infections.

Indication	Daily dose regimen (according to severity)	Duration of treatment (according to severity)
Complicated UTI	200 mg twice daily (can be increased to 400 mg twice daily)	7-21 days
Pyelonephritis	200 mg twice daily (can be increased to 400 mg twice daily)	7-10 days (can be extended to 14 days)

Acute prostatitis Chronic prostatitis	200 mg twice daily (can be increased to 400 mg twice daily)	2-4 weeks* 4-8 weeks*
Epididymo-orchitis	200 mg twice daily (can be increased to 400 mg twice daily)	14 days
Pelvic inflammatory disease	400mg twice daily	14 days

* for prostatitis longer duration of treatment may be considered after careful re- examination of the patient.

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

Ofloxacin solution is only intended for SLOW intravenous infusion; it is administered once or twice daily. The infusion time for Ofloxacin IV should not be less than 30 minutes for 200 mg. 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. Generally, individual doses are to be given at approximately equal intervals.

Posology in patients with renal insufficiency

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

CREATININE CLEARANCE	UNIT DOSE mg*	NUMBER / 24 h	INTERVALS h
50 – 20 ml/min	100 – 200	1	24
< 20 ml/min** or haemodialysis or peritoneal dialysis	100 or 200	1 1	24 48

* According to indication or dose interval.

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

When creatinine clearance cannot be measured, it can be estimated with reference to the serum creatinine level using the following Cockcroft's formula for adults:

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

or

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

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

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.

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

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)

Duration of treatment: The duration of treatment is determined according to the response of the causative organisms and the clinical picture. As with all antibacterial agents, treatment with Ofloxacin should be continued for at least 3 days after the body temperature has returned to normal and the symptoms have subsided.

In most cases of acute infection, a course of treatment lasting 7 to 10 days is sufficient. Once the patient's condition has improved, the mode of administration should be changed from parenteral to oral, normally at the same total daily dose.

Treatment should not exceed 2 months duration.

4.3 Contraindications

• Hypersensitivity to the active substance, other quinolones or to any of the excipients listed in section 6.1.

• Ofloxacin should not be used in patients with a past history of tendinitis related to fluoroquinolone administration.

• Ofloxacin, like other 4-quinolones, is contra-indicated in patients with a history of epilepsy or with a lowered seizure threshold.

• Ofloxacin is contra-indicated in children or growing adolescents, and in pregnant or breast-feeding women, since animal experiments do not entirely exclude the risk of damage to the cartilage of joints in the growing subject.

• Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

4.4 Special warnings and precautions for use

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

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

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

Escherichia coli infection

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.

Neisseria gonorrhoeae infections

Due to increase in resistance to N. gonorhoeae, ofloxacin should not be used as empirical treatment option in suspected gonococcal infection (urethral gonococcal infection, pelvic inflammatory disease and epididymo-orchitis), unless the pathogen has been identified and confirmed as susceptible to ofloxacin. If clinical improvement is not achieved in 3 days of treatment, the therapy should be reconsidered.

Pelvic inflammatory disease

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

Hypersensitivity and allergic reactions

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

Severe bullous reactions

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

Clostridium difficile-associated disease

Diarrhoea, 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 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 otherquinolones, 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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

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

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

Patients with renal impairment

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

QT interval prolongation

Very rare cases of QT interval prolongation have been reported in patients taking fluoroquinolones. Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

• congenital long QT syndrome

• concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

• uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)

• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

• Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including Ofloxacin, in these populations.

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

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients with history of psychotic disorder

Psychotic reactions have been reported in patients receiving fluoroquinolones. In some cases these have progressed to suicidal thoughts or self-endangering behaviour including suicide attempt, sometimes after a single dose (see section 4.8). In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted.

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

Patients with impaired liver function

Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, 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

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

Prevention of photosensitisation

Photosensitisation has been reported with ofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation

Superinfection

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

Peripheral neuropathy

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

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In these diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate-dehydrogenase deficiency may be predisposed to haemolytic reactions if they are treated with quinolones. Therefore, if ofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an 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

Drugs known to prolong QT interval

Ofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti- arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (See section 4.4).

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

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

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

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

Glibenclamide

Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; patients treated with this combination should be closely monitored.

Probenecid, cimetidine, furosemide and 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 co-administered with drugs that affect the tubular renal secretion such as probenecid, cimetidine, furosemide and methotrexate.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with ofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should be monitored in patients treated with vitamin K antagonists (see section 4.4) because of a possible increase in the effect of coumarin derivatives.

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: Contraindications)

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Since there have been occasional reports of somnolence, impairment of skills, dizziness and visual disturbances, patients should know how they react to Ofloxacin before they drive or operate machinery. These effects may be enhanced by alcohol.

4.8 Undesirable effects

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from available data)****
Infections and infestations		Fungal infection, Pathogen resistance			
Blood and the lymphatic system disorders				Anaemia Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis Bone marrow failure
Immune system disorders			Anaphylactic reaction**, Anaphylactoid reaction**,	Anaphylactic shock**, Anaphylactoid shock**	

			Angioedema**		
Metabolism and Nutrition disorders			Anorexia		Hypoglycaemia in diabetics treated with hypoglycaemic agents (see Section 4.4) Hyperglycaemia Hypoglycaemic coma
Psychiatric Disorders*		Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt (see Section 4.4) Nervousness
Nervous system disorders*		Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy** Peripheral sensory motor neuropathy** Convulsion**,	Tremor Dyskinesia Ageusia Syncope Benign

				Extra-pyramidal symptoms or other disorders of muscular coordination	intracranial hypertension (Pseudotumor cerebri).
Eye disorders*		Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders*		Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders			Tachycardia		Ventricular arrhythmias, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)
Vascular disorders	*applies onlytothe solution for infusion*:		Hypotension		*appliesonlyto thesolutionfor infusion*: During infusion of

	Phlebitis				ofloxacin, tachycardia and hypotension may occur. Such a decrease in blood pressure may, in very rare cases, be severe.
Respiratory, thoracic and mediastinal disorders		Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastro- intestinal disorders		Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudo-membranous colitis* Jaundice cholestatic	Dyspepsia Flatulence Constipation Pancreatitis
Hepato-bilary disorders			Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase)		Hepatitis, which may be severe**; Severe liver injury, including cases of acute liver failure, sometimes fatal, have been reported with

			Blood bilirubin increased		ofloxacin, primarily in patients with underlying liver disorders (see section 4.4)
Skin and subcutaneous tissue disorders		Pruritus, Rash	Urticaria, Hot flushes, Hyperhidrosis Pustular rash	Erythema multiforme, Toxic epidermal necrolysis, Photo-sensitivity reaction**, Drug eruption Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis	Stevens-Johnson syndrome; Acute generalized exanthemous pustulosis; drug rash Stomatitis; Exfoliative dermatitis
Musculoskeletal and Connective tissue disorders*			Tendonitis	Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be	Rhabdomyolysis and/or Myopathy, Muscular weakness Muscle tear, muscle rupture

				bilateral.	Ligament rupture Arthritis
Renal and Urinary disorders			Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital and familial/genetic disorders					Attacks of porphyria in patients with porphyria
General disorders and administration site conditions*	*applies onlytothe solution for infusion*: Infusion site reaction (pain, reddening)				Asthenia Pyrexia Pain (including pain in the back, chest and extremities)

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

** postmarketing experience

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

Elimination of ofloxacin may be increased by forced diuresis.

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: Quinolone antibacterials, Fluoroquinolones. ATC code J01M A01

Mechanism of action

Ofloxacin is a quinolone-carboxylic acid derivative with a wide range of antibacterial activity against both Gram-negative and Gram-positive organisms.

The primary mode of action of the quinolones is the specific inhibition of bacterial DNA gyrase. This enzyme is required for DNA replication, transcription, repair and recombination. Its inhibition leads to expansion and destabilisation of the bacterial DNA and hence to cell death.

It appears that certain quinolones, including ofloxacin, have a second non RNA dependent action on bacterial cells, which enhances bactericidal effectiveness. The nature of this second action has not yet been clarified.

PK/PD relationship

Fluoroquinolones have a concentration-dependent bactericidal activity, with a moderate post antibiotic effect. For this class of antimicrobials, the ratio between AUC and MIC or Cmax and MIC is predictive of clinical success.

Mechanisms of resistance

Resistance to ofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to ofloxacin.

Susceptibility testing breakpoints

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains.

Breakpoints set by EUCAST:

MIC breakpoint (mg/L)		
Microorganism	**Susceptible ≤**	**Resistant >**
Enterobacteriaceae	0.5	1
Staphylococcus spp.	1	1[a]
Streptococcuspneumoniae[b]	0.125	4
Haemophilusinfluenzae	0.5	0.5
Moraxella catarrhalis	0.5	0.5
Neisseria gonorrheae	0.125	0.25

a. Breakpoints relate to high dose therapy

b. Wild type *S. pneumonia* are not considered susceptible to ofloxacin and are therefore categorized as intermediate

Susceptibility

The prevalence of resistance may vary geographically and over 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 questionable.

Commonly susceptible species, including microorganisms with intermediate susceptibility
AerobicGram-positivemicro-organisms *Bacillus anthracis* *Bordetella pertussis* Corynebacteria *Streptococci*
AerobicGram-negativemicro-organisms Campylobacter Enterobacter *Haemophilus influenzae Legionella pneumophila Moraxella catarrhalis Morganella morganii Proteus vulgaris* Salmonella Shigella Yersinia
Othermicro-organisms Chlamydia *Chlamydophila pneumonia Mycoplasma hominis Mycoplasma pneumoniae Ureaplasma urealyticum*
Species for which acquired resistance may be a problem
AerobicGram-positivemicro-organisms *Staphylococci coagulase negative Staphylococcus aureus (methicillin-sensitive) Streptococcus pneumoniae*
AerobicGram-negativemicro-organisms *Acinetobacter baumannii*
Citrobacter freundii Escherichia coli Klebsiella oxytoca Klebsiella pneumoniae Neisseria gonorrhoeae Proteus mirabilis Pseudomonas aeruginosa Serratia

Inherently resistant organisms
AerobicGram-positivemicro-organisms Enterococci *Listeria monocytogenes* Nocardia Staphylococci methi-R
Anaerobic micro-organisms Bacteroides spp. *Clostridium difficile*

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

5.2 Pharmacokinetic properties

Maximum plasma concentrations occur within five minutes of the end of the infusion. The peak serum concentration, after a single oral dose of 200 mg, averages 2.5 to 3µg/ml within one hour. The serum elimination half-life is 6-7 hours and is linear. The apparent volume of distribution is 120 litres. Following multiple dosing, the serum concentration is not significantly increased (multiplication factor approximately 1.5). Ofloxacin concentrations in the urine and at the site of urinary tract infections exceed those measured in serum by 5 to 100-fold. Ofloxacin is primarily excreted unchanged in the urine.

Urinary clearance is reduced in renal insufficiency.

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride Hydrochloric acid Water for injections

6.2 Incompatibilities

Ofloxacin IV should be administered alone unless compatibility with other infusion fluids has been demonstrated. Compatible infusion solutions include isotonic sodium chloride, Ringer's solution and 5 % glucose solution. Heparin and ofloxacin are incompatible.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Ofloxacin IV presented in glass infusion bottles should be protected from light.

6.5 Nature and contents of container

Clear, colourless Type I glass vials with grey chlorobutyl rubber closures and aluminium caps containing either 50 ml, 100ml infusion solution.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.

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