sanofi aventis **Tarivid® i.v. 200 mg**

1. NAME OF THE MEDICINAL PRODUCT

Tarivid® i.v. 200 mg
Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle with 100 ml solution for infusion contains 220 mg ofloxacin hydrochloride as the active substance, equivalent to 200 mg ofloxacin.

Excipient with known effect: sodium chloride.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tarivid is suitable for the treatment of the following bacterial infections, if they have been caused by pathogens sensitive to ofloxacin:

- acute, chronic and recurrent respiratory tract infections (bronchitis), caused by *Haemophilus influenzae* or other gram-negative and multi-resistant pathogens and by *Staphylococcus aureus.*
- pneumonia, particularly caused by problem micro-organisms such as Escherichia coli, Klebsiella, Enterobacter, Proteus, Pseudomonas, Legionella and Staphylococcus. As pneumonia in non-hospitalised patients is mainly caused by pneumococci, Tarivid is not recommended as first-line therapy in such cases.
- chronic and recurrent ear, nose and throat infections, particularly if caused by gram-negative micro-organisms, including Pseudomonas, or caused by Staphylococcus. Tarivid is thus not indicated in the treatment of acute angina tonsillaris caused by beta-haemolytic streptococci (see also section 4.2).
- skin and soft-tissue infections.
- bone infections (osteitis, osteomyelitis).
- infections of the abdominal cavity, including the lesser pelvis, and bacterial diarrhoea requiring antibiotic treatment.
- renal and genitourinary infections, gonorrhoea.
- septic infections.

Ofloxacin has no activity against *Treponema pallidum*.

The usual and generally recognised guidelines for the appropriate use of antibiotics should be adhered to during the administration of Tarivid.

4.2 Posology and method of administration

The dosage, method and duration of administration depend on the nature and severity of the infection.

Dosage in patients with normal renal function

Therapeutic indications	Single and daily doses
Urinary tract infections	1 x 100 mg to 2 x 100 mg (or 1 x 200 mg) ofloxacin daily
Renal and genital infections	2 x 100 mg to 2 x 200 mg ofloxacin daily
Respiratory tract infections and ear, nose and throat infections	2 x 200 mg ofloxacin daily
Skin and soft-tissue infections	2 x 200 mg ofloxacin daily
Bone infections	2 x 200 mg ofloxacin daily
Infections of the abdominal cavity (including bacterial diarrhoea)	2 x 200 mg ofloxacin daily
Septic infections	2 x 200 mg ofloxacin daily

In individual cases, it may be necessary to increase the dose when treating pathogens with varying sensitivity, in severe infections (e.g. of the respiratory tract or bones) or if the patient response is insufficient. In such cases, the dose can be increased to 400 mg ofloxacin twice daily. The same applies in infections with confounding co-factors.
It is important to maintain approximately equal dosing intervals.

Children and adolescents
Ofloxacin must not be used in children and adolescents (see section 4.3).

Elderly patients
Apart from the need to consider possible impaired renal function, no dose adjustment is required for elderly patients (see section 4.4 QT interval prolongation).

Dosage in patients with impaired renal function
For patients with moderately and severely impaired renal function, determined as creatinine clearance or as serum creatinine, the following dosage is suggested:

The dose should be reduced as follows:

Creati-nine clea-rance	Unit dose*	Interval
50 to 20 ml/ min	100 to 200 mg	24 hours
≤ 20 ml/ min** or Haemo-dialysis or peri-toneal dialysis	100 mg or 200 mg	24 hours 48 hours

*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:
ClCr [ml/min] = {weight [kg] x (140 – age [in years])} / (72 x serum creatinine [mg/dl])
or
ClCr [ml/min] = {weight [kg] x (140 – age [in years])} / (0.814 x serum creatinine [µmol/l])

Women:

ClCr [ml/min] = 0.85 x (above value)

In individual cases (see above) however, it may be necessary to increase the above dose.

Dosage in patients with impaired hepatic function
In patients with severely impaired hepatic function (e.g. cirrhosis of the liver with ascites), elimination of ofloxacin may be reduced. In such cases, it is therefore recommended that a maximum daily dose of 400 mg ofloxacin should not be exceeded.

Method of administration
Tarivid IV is intended for use in **slow** intravenous infusions. An infusion time of at least 30 minutes per 200 mg ofloxacin must be allowed. This particularly applies if ofloxacin is administered concurrently with medicines which can reduce blood pressure or with barbiturate anaesthetics.

Tarivid IV can be mixed with the following solutions:
Isotonic sodium chloride solution, Ringer's solution and 5% glucose solution.

Tarivid IV may only be mixed with other solutions whose compatibility has been confirmed.

Heparin and Tarivid IV may not be mixed.

Tarivid IV should be administered as a freshly opened solution only.
Once the patient's condition has improved, treatment can be switched from the solution for infusion to tablets at the same dose.

Duration of treatment
Duration of treatment depends upon the pathogenic response and the clinical picture. In general, treatment should be continued for at least 2 to 3 days after fever and other symptoms have subsided.

In acute infections, a treatment period of 7 to 10 days is usually sufficient. The usual duration of treatment in cases of salmonellosis is 7 to 8 days, in cases of shigellosis 3 to 5 days and in cases of intestinal infections with *Escherichia coli*, 3 days.

For uncomplicated lower urinary tract infections, a treatment period of 3 days is usually sufficient.

In infections of the bones, duration of treatment is 3 to 4 weeks and may be longer in individual cases.

If sensitivity is confirmed and infections with beta-haemolytic streptococci (e.g. erysipelas) are being treated, the treatment must be continued for at least 10 days, in order to prevent sequelae such as rheumatic fever or glomerulonephritis. As beta-haemolytic streptococci vary in their sensitivity to ofloxacin, however, treatment of such infections requires confirmation of sensitivity in individual cases.

Until further data are available, a treatment period of 2 months should not be exceeded.

4.3 Contraindications

Tarivid must not be administered:
- in patients who are hypersensitive to ofloxacin, other quinolones or any of the excipients listed in section 6.1,
- in patients with epilepsy or a lowered CNS seizure threshold,
- in patients with tendon disease/damage associated with previous quinolone therapy,
- in children and adolescents up to 18 years of age*,
- during pregnancy*,
- during lactation*.

*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

Methicillin-resistant S. aureus
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).

E. coli
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.

Pneumococci or Mycoplasma spp.
Ofloxacin is not the antibiotic of first choice in the treatment of pneumonia caused by pneumococci or *Mycoplasma* spp. Particularly in severe forms of pneumococcal pneumonia, ofloxacin may not guarantee optimal antibiotic therapy.

P. aeruginosa
Nosocomial and other severe infections caused by *P. aeruginosa* may require combination therapy. In cases of specific infections caused by *P. Aeruginosa* in particular, resistance levels must be tested in order to ensure targeted therapy.

Streptococci
Tarivid is not indicated for the treatment of acute angina tonsillaris caused by beta-haemolytic streptococci.

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 reactions
Hypersensitivity and allergic reactions following the initial administration of fluoroquinolones have been reported. Anaphylactic and anaphylactoid reactions may progress to life-threatening shock, even after the initial administration. In this case, ofloxacin must be discontinued and appropriate emergency procedures (e.g. shock treatment, including administration of antihistamines, corticosteroids, sympathomimetics and, if required, ventilation) must be initiated.

Diseases caused by Clostridium difficile
The occurrence of diarrhoea, particularly if it is severe, persistent and/or contains blood, during or after treatment with Tarivid (including several weeks after treatment), may indicate a disease triggered by *Clostridium difficile* (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 pseudomembranous colitis is suspected, treatment with Tarivid must be discontinued immediately and an appropriate therapy initiated without delay (e.g. oral treatment with specific antibiotics/chemotherapeutic agents, as oral vancomycin, oral teicoplanin or metronidazole, with proven clinical efficacy). Medicines that inhibit intestinal peristalsis must not be taken.

Patients with a tendency for seizures
Quinolones may lower the seizure threshold and may trigger seizures. Tarivid is contraindicated in patients with known epilepsy or a known lowered CNS seizure threshold (see section 4.3). As with other quinolones, Tarivid should be used only with extreme caution in patients otherwise predisposed to epileptic seizures, e.g. patients with existing CNS lesions, during concurrent treatment with fenbufen or comparable non-steroidal anti-inflammatory drugs, or with medicines that lower the seizure threshold, such as theophylline (see also section 4.5).

Treatment with Tarivid must be discontinued at the onset of seizures. Appropriate standard emergency procedures are indicated (e.g. maintenance of airway patency and administration of anticonvulsants such as diazepam or barbiturates).

Tendinitis
Rarely, tendinitis has been observed during quinolone therapy, which may lead to tendon rupture in some cases, particularly of the Achilles tendon. Tendinitis 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 tendinitis 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 tendinitis. If tendinitis is suspected, treatment with Tarivid must be immediately discontinued and the affected tendon treated appropriately (e.g. by immobilisation) (see section 4.3 and 4.8).

Patients with impaired renal function
Ofloxacin is mainly excreted via the kidneys. In patients with impaired renal function, Tarivid should therefore only be administered after a dose adjustment (see section 4.2), together with medical monitoring of the renal function.

Psychotic reactions
During treatment with quinolones including ofloxacin, depression and psychotic reactions have been reported in patients. In some cases these have developed into suicidal ideation and self-endangering behaviour including suicide attempt (see section 4.8) – sometimes already after a single dose of ofloxacin. If the patient should develop such reactions, ofloxacin must be discontinued immediately and appropriate measures initiated. Caution should be exercised if ofloxacin is used in patients with psychotic disorders or a medical history of psychiatric disorders.

Patients with impaired hepatic function
Hepatic damage may occur during treatment with Tarivid. In patients with impaired hepatic function, Tarivid should be administered only if hepatic function is medically monitored. Cases of fulminant hepatitis, which may lead to liver failure (sometimes fatal), have been reported with fluoroquinolones. Patients should be instructed to suspend treatment and seek advice from their doctor if signs of hepatic disease develop, e.g. loss of appetite, jaundice, dark discolouration of the urine, pruritus or abdominal tenderness (see section 4.8).

Patients on treatment with vitamin K antagonists
Due to a possible increase in coagulation values (PT/INR) and/or bleeding in patients on concomitant treatment with fluoroquinolones, including ofloxacin, and a vitamin K antagonist (e.g. warfarin), coagulation values should be monitored (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.

Secondary infection
As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. The patient's condition should therefore be monitored at regular intervals. Appropriate measures must be taken if a secondary infection occurs.

Heart disorders
Very rare cases of QT interval prolongation have been reported in patients taking fluoroquinolones.
When using fluoroquinolones, including ofloxacin, caution should be taken in patients with known risk factors for QT interval prolongation, for example:
- congenital long QT syndrome,
- concomitant administration of other medicines that are known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic and tetracyclic antidepressants, macrolides, imidazole, antifungal agents and antimalarial agents, some non-sedative antihistamines [e.g. astemizole, terfenadine, ebastine], antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia),
- elderly patients,
- cardiac disease (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 also sections 4.2 "Elderly patients", 4.5, 4.8 and 4.9).

Dysglycaemia
As with all quinolones disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in patients with diabetes who have received concomitant treatment with an oral antidiabetic agent (e.g. glibenclamide) or insulin. Cases of hypoglycaemic coma have been reported. Careful monitoring of blood glucose levels is recommended in such patients with diabetes (see section 4.8).

Peripheral neuropathy
During treatment with fluoroquinolones, including ofloxacin, sensory or sensorimotor peripheral neuropathies have been reported, the onset of which may be rapid (see section 4.8). If patients develop symptoms of neuropathy, ofloxacin should be discontinued. This would minimize the possible risk of developing an irreversible condition.

Patients with glucose-6-phosphate dehydrogenase deficiency
Patients with latent or manifest 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 or porphyrin in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Other notes
Patients who have reacted to other quinolones with severe undesirable effects (e.g. severe neurological reactions) are at greater risk of experiencing similar reactions to ofloxacin.

If, during the infusion, severe hypotension should occur, the infusion must be discontinued immediately.

Tarivid contains lactose
One bottle (100 ml) contains 15.4 mmol (354 mg) sodium. This should be considered in persons on a sodium-controlled (low-sodium/low-salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

If Tarivid IV is administered concurrently with medicines that have a potentially antihypertensive effect, a sudden fall in blood pressure may occur. In such cases, and in patients undergoing concurrent administration of barbiturate anaesthetics, monitoring of cardiovascular function is therefore indicated.

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.

Medicinal products that prolong the QT-interval

Ofloxacin, like other quinolones, should be used with caution in patients taking medicines known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic and tetracyclic antidepressants, macrolides, imidazole antifungal agents and antimalarial agents, some non-sedative antihistamines [e.g. astemizole, terfenadine, ebastine], antipsychotics) (see also 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). Close monitoring of the coagulation status of patients undergoing concurrent treatment with coumarin derivatives is thus recommended.

Glibenclamide

Ofloxacin can cause a slight increase in serum glibenclamide levels. As hypoglycaemia is then more likely to occur, particularly close monitoring of blood glucose levels is thus recommended with concomitant administration of ofloxacin and glibenclamide.

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 coadministered with drugs that affect the tubular renal secretion such as probenecid, cimetidine, furosemide and methotrexate, because it can cause elevated serum levels and increased undesirable effects.

4.6 Pregnancy and lactation

Pregnancy

There are no sufficient data in humans on the administration of ofloxacin to pregnant women. 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. In juvenile and unborn animals with quinolone exposition effects on the immature cartilage have been observed but no teratogenic effects. It can not be excluded that the medicinal product causes damage to joint cartilage of the childlike or juvenile organism/fetus.

Tarivid is therefore contra-indicated in the pregnancy (see section 4.3 and 5.3).

Lactation

Small amounts of ofloxacin are excreted in breast milk. Due to possible risk of arthropathy and other serious toxicity in the nursing infant, breast feeding should be discontinued during treatment with Tarivid (see section 4.3 and 5.3).

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. vertigo/dizziness, drowsiness, visual disturbances) can impair the patient's ability to concentrate and responsiveness and, as a result, can present a risk in situations in which these abilities are of particular importance (e.g. driving a vehicle, operating machinery). This is enhanced in association with alcohol. Patients should therefore observe their reactions to treatment before driving a vehicle or operating machinery.

4.8 Undesirable effects

The following data are based on clinical studies and extensive post-marketing experience.

See table below and on pages 5 and 6.

Notes

Apart from very rare cases (e.g. isolated cases of disorders of smell, taste and hearing), observed undesirable effects have resolved after the discontinuation of Tarivid.

Some undesirable effects (e.g. pseudomembranous colitis, hypersensitivity reactions, seizures) may be acutely life-threatening in some cases and require immediate countermeasures (see also section 4.4).

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 Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

Symptoms of intoxication

The main symptoms of acute overdose can include (amongst others) central nervous symptoms, such as confusion, dizziness, clouding of consciousness and seizures, increase in QT interval as well as gastrointestinal complaints, such as nausea and erosions of the gastrointestinal mucosa.

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

Treatment of intoxication
In case of overdose a symptomatic treatment should be initiated. ECG monitoring should be performed due to the possibility of QT interval prolongation. It may be necessary to monitor and secure organ and vital functions in an intensive care unit.
If seizures occur, immediate treatment with anticonvulsives is recommended.
In the event of a massive overdose, ofloxacin elimination can be increased by forced diuresis.
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
Ofloxacin is a bactericidal antibiotic from the fluoroquinolone group

ATC code
J01MA01

Mechanism of action
The mechanism of action of ofloxacin is based on impairment of DNA synthesis, by inhibiting bacterial topoisomerase II (gyrase) and topoisomerase IV, resulting in a bactericidal effect.

Pharmacokinetic/pharmacodynamic relationship
Efficacy is primarily dependent on the ratio between the peak serum level (C_{max}) and the minimum inhibitory concentration (MIC) of the pathogen concerned, or the ratio between AUC (area under the curve) and the MIC of the pathogen concerned.

Resistance mechanisms
Resistance to ofloxacin can be based on the following mechanisms:
- Target structure changes: The most common mechanism of resistance to ofloxacin and other fluoroquinolones consists of changes to topoisomerase II or IV as a result of mutation.
- Other resistance mechanisms lead to a decrease in fluoroquinolone concentration at the site of action. This is due to reduced cell penetration as a result of decreased porin formation, or increased secretion from the cell by efflux pumps.
- Transferable, plasmid-coded resistance has been demonstrated for *Escherichia coli* and *Klebsiella* spp.

With ofloxacin, there is partial or complete cross-resistance with other fluoroquinolones.

Breakpoints
Ofloxacin is tested using the standard dilution series. Minimum inhibitory concentrations for sensitive and resistant microbes have been established as follows:
EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

	sensitive	resistant
Enterobacte-riaceae	≤ 0.5 mg/l	> 1 mg/l
Staphylococ-cus spp.	≤ 1 mg/l	> 1 mg/l
Streptococcus pneumoniae	≤ 0.12 mg/l	> 4 mg/l
Haemophilus influenzae	≤ 0.5 mg/l	> 0.5 mg/l
Moraxella catarrhalis	≤ 0.5 mg/l	> 0.5 mg/l
Neisseria gonorrhoeae	≤ 0.12 mg/l	> 0.25 mg/l
non-species-specific breakpoints[1)]*	≤ 0.5 mg/l	> 1 mg/l

1)Limits refer to an oral dose of 200 mg x 2 to 400 mg x 2 and an intravenous dose of 200 mg x 2 to 400 mg x 2.
*mainly based on serum pharmacokinetics.

Prevalence of acquired resistance
The prevalence of acquired resistance may vary geographically and over time for individual species. Local information on resistance is therefore required, particularly for the adequate treatment of severe infections. Expert therapeutic advice should be sought if the local resistance situation is such that the efficacy of ofloxacin is questionable. Particularly in the case of serious infections or treatment failure, a microbiological diagnosis – with detection of the pathogen and its susceptibility to ofloxacin – should be sought.
Prevalence of acquired resistance in Germany - based on data obtained over the past 5 years from national resistance monitoring projects and studies (status as of December 2013)

Normally susceptible species
Aerobic gram-positive micro-organisms
Staphylococcus saprophyticus°
Streptococcus pyogenes
Aerobic gram-negative micro-organisms
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus influenzae
Legionella pneumophila°

System organ class	Common (>1/100, <1/10)	Uncommon (≥ 1/1,000, < 1/100)	Rare (≥ 1/10,000, < 1/1,000)	Very rare (< 1/10,000)	Frequency not known (cannot be estimated from the available data)*
Infections and infestations		Increase in resistant bacteria and fungi (see section 4.4)			
Blood and lymphatic system disorders				Anaemia, haemolytic anaemia, leukopenia, eosinophilia, thrombocytopenia, pancytopenia	Agranulocytosis, bone marrow depression
Immune system disorders			Anaphylactic / anaphylactoid hypersensitivity reactions*, angioedema*	Vasculitis that affects inner organs, anaphylactic / anaphylactoid shock*	
Metabolism and nutrition disorders			Loss of appetite		Hyperglycaemia, hypoglycaemia, particularly in patients treated with antidiabetics (see section 4.4), hypoglycaemic coma
Psychiatric disorders		Agitation, sleep disorders, insomnia	Psychotic reactions (e.g. with hallucinations), anxiety, confusion, intensive dreaming (and even nightmares), depression		Psychotic reactions and depression with self-harm to the point of suicidal ideation or acts (see section 4.4), nervousness
Nervous system disorders		Agitation, headache, dizziness	Somnolence, sensory disorders such as paraesthesias (e.g. hypoaesthesia or hyperaesthesia), disturbances of taste and smell (including anosmia)	Sensory or sensorimotor peripheral neuropathy*, seizures*, extrapyramidal symptoms or other muscular co-ordination disorders (see section 4.4)	Tremor, dyskinesia, ageusia, syncope
Eye disorders		Eye irritation, burning sensation in the eyes, conjunctivitis	Visual disturbances (e.g. blurred vision, diplopia and chromatopsia)		
Ear and labyrinth disorders		Vertigo	Imbalance	Tinnitus, loss of hearing	Hearing disorders
Cardiac disorders		Palpitations	Tachycardia		ventricular arrhythmias and torsade de pointes (especially reported in patients at risk of QT-prolongation), ECG-QT interval prolongation (see sections 4.4 and 4.9)
Vascular disorders	Phlebitis		Hypotension, hypertension		Severe hypotension to the point of collapse with loss of consciousness (see also section 4.4).
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)	**Frequency not known** (cannot be estimated from the available data)*

System organ class	Common (>1/100, <1/10)	Uncommon (≥ 1/1,000, < 1/100)	Rare (≥ 1/10,000, < 1/1,000)	Very rare (< 1/10,000)	Frequency not known (cannot be estimated from the available data)*
Respiratory, thoracic and mediastinal disorders		Dry cough, naso-pharyngitis, runny nose	Dyspnoea, bronchospasm		Allergic pneumonitis, severe dyspnoea
Gastrointestinal disorders		Gastric upset, abdominal pain, diarrhoea, nausea, vomiting	Enterocolitis sometimes with haemorrhage)	Pseudomembranous colitis* (see section 4.4)	Dyspepsia, flatulence, constipation, pancreatitis
Hepatobiliary disorders			Impairment of hepatic function with elevation of liver enzymes (ALAT, ASAT, LDH, gamma-GT, alkaline phosphatase) and/or bilirubin	Cholestatic jaundice	Hepatitis, severe hepatic damage*
Skin and subcutaneous tissue disorders		Cutaneous reactions such as pruritus, rash	Hot flushes, sweating, urticaria, vesicular or pustular rash	Serious mucocutaneous reactions (erythema multiforme, toxic epidermal necrolysis), photosensitivity (sunburn-like symptoms, discolouration or detachment of the nails), vascular purpura, vasculitis, which may lead to skin necrosis in isolated cases.	Stevens-Johnson syndrome, acute generalised exanthemous pustulosis, fixed drug exanthema, drug rash, stomatitis
Musculoskeletal and connective tissue disorders			Tendinitis	Articular and muscular complaints (e.g. pain), tendon rupture (e.g. of the Achilles tendon), see also section 4.4. Which may occur within 48 hours of treatment start and may be bilateral.	Rhabdomyolysis and/or myopathy, muscle weakness (of particular significance in patients with myasthenia gravis), muscle tear, muscle rupture, ligament rupture, arthritis
Renal and urinary disorders			Impairment of renal function (e.g. with a rise in 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	Injection-site pain and redness, phlebitis				Asthenia, pyrexia, pain (including pain in back, chest, and extremities)

*postmarketing experience

Moraxella catarrhalis
Morganella morganii
Proteus vulgaris
Salmonella enterica (enteritis salmonellae only)
Serratia marcescens
Other micro-organisms
Chlamydophila pneumoniae°$
Chlamydia trachomatis°$

Mycoplasma hominis°$
Mycoplasma pneumoniae°$
Ureaplasma urealyticum°$
Species in which acquired resistance may pose a problem during use
Aerobic gram-positive micro-organisms
Enterococcus faecalis
Staphylococcus aureus (methicillin-sensitive)
Staphylococcus aureus (methicillin-resistant)+
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis+
Streptococcus pneumoniae$
Aerobic gram-negative micro-organisms
Acinetobacter baumannii$
Campylobacter jejuni$
Citrobacter freundii
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa$
Stenotrophomonas maltophilia$
Naturally resistant species
Aerobic gram-positive micro-organisms
Enterococcus faecium
Anaerobic micro-organisms
Bacteroides spp.
Clostridium difficile

The above categories are almost exclusively based on data on ciprofloxacin and levofloxacin.

° At the time this table was published, no updated data were available. Sensitivity is assumed in the primary literature, standard works and therapeutic guidelines.

$ The natural susceptibility of most isolates is in the intermediate range.

+ The resistance rate is more than 50% in at least one region.

5.2 Pharmacokinetic properties

Following oral administration in fasting volunteers, ofloxacin is rapidly and almost completely absorbed. The mean peak serum concentration following a single oral dose of 200 mg is 2.6 µg/ml and is reached within 1 hour. The serum elimination half-life is 5.7 to 7.0 hours and is dose-independent. The apparent volume of distribution is 120 litres. Following multiple administration of ofloxacin, the serum concentration does not increase significantly (accumulation factor following twice-daily administration: 1.5). Plasma protein binding is approximately 25%. Less than 5% of ofloxacin undergoes biotransformation.

The two major metabolites which are recovered in the urine are N-desmethyl-ofloxacin and ofloxacin-N-oxide. Elimination is mainly renal. 80 to 90% of the dose are recovered in the urine as unchanged substance. Ofloxacin is recovered in the bile in glucuronidated form. In patients with renal insufficiency, the serum half-life is prolonged; total and renal clearance decrease according to the creatinine clearance.

The pharmacokinetics of ofloxacin following intravenous infusion closely resembles that following oral administration. The following table shows pharmacokinetic parameters following infusion of ofloxacin.

	Dose	
	100 mg ofloxacin	200 mg ofloxacin
Half-life (min)	280	285
Total clearance (ml/min)	272	258
Renal clearance (ml/min)	237	215
Urinary excretion (% of the dose after 24 hours)	85	81

The following mean serum concentrations were determined:

Dose	After the end of infusion	After 4 hours	After 12 hours
100 mg	2.9 mg/l	0.5 mg/l	0.2 mg/l
200 mg	5.2 mg/l	1.1 mg/l	0.3 mg/l

5.3 Preclinical safety data

Ofloxacin has a neurotoxic potential and causes reversible testicular changes at high doses. Furthermore, preclinical studies with single and repeated administration in adult animals and pharmacological safety studies have shown no indications of any further specific risks associated with ofloxacin administration.

In common with other gyrase inhibitors, ofloxacin can precipitate damage to the large, weight-bearing joints of juvenile animals during the growth phase. The extent of cartilage damage is age-, species- and dose-dependent and can be considerably reduced by relieving pressure on the joints.

Ofloxacin has no effect on fertility or perinatal and postnatal development and causes no teratogenic or other embryotoxic effects in animal studies at therapeutic doses.

No conventional long-term carcinogenicity studies have been performed for ofloxacin. In *in vitro* and *in vivo* studies, ofloxacin was shown to be non-mutagenic. Data on the phototoxicity, photomutagenicity and photocarcinogenicity of ofloxacin show only a weak photomutagenic or phototumorigenic effect *in vitro* or *in vivo* compared with other fluoroquinolones.

There are no indications of any cataractogenic or cocataractogenic effect following ofloxacin exposure. Some gyrase inhibitors are known to possess a potential for prolongation of the QT interval. Preclinical studies to date showed that ofloxacin has only a weak potential for prolongation of the QT interval compared with the aforementioned gyrase inhibitors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, hydrochloric acid 3.6% for pH adjustment, water for injections

6.2 Incompatibilities

Tarivid IV 200 mg may not be mixed with heparin.

6.3 Shelf life

3 years.
The solution for infusion should be used immediately after opening the infusion bottle.

6.4 Special precautions for storage

Store in the original packaging in order to protect from light.

6.5 Nature and contents of container

Clear glass bottles with rubber stopper and flanged aluminium cap in packs with 5 bottles, each containing 100 ml solution for infusion.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

24720.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22. April 1993

Date of latest renewal: 28. June 2001

10. DATE OF REVISION OF THE TEXT

August 2014

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

* €0.06 per call (fixed network Germany); max. €0.42 /min (mobile communications)

Direct all enquiries to:

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