film-coated tablets

**Presentation**
Tarivid 200 film-coated tablets

**Composition**
Substance or indication group: Broad-spectrum antibiotic, gyrase inhibitor (quinolone derivative).
Pharmacologically active ingredient: 1 film-coated tablet contains 200 mg ofloxacin.
Other ingredients: Lactose, magnesium stearate, macrocol 8000, colouring E 171, talcum, maize starch, hydroxypropyl cellulose, carboxymethylcellulose, methyl hydroxypropyl cellulose.

**Indications**
Tarivid 200 film-coated tablets 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 multiresistant pathogens or by Staphylococcus aureus
- Pneumonia, especially caused by problem pathogens such as Escherichia coli, Klebsiella, Enterobacter, Proteus, Pseudomonas, Legionella, Staphylococcus. Since pneumonia in the outpatient sphere is predominantly caused by pneumococci, Tarivid 200 film-coated tablets is not first-line therapy in these cases
- Chronic and recurrent infections of the ear, nose and throat, especially if they are caused by Gram-negative organisms including Pseudomonas, or by Staphylococcus. Hence Tarivid 200 film-coated tablets is not indicated for the treatment of acute quinsy caused by beta-haemolytic streptococci (see “Administration and duration of use”)
- Infections of the soft tissues and skin
- Infections of the bones (osteitis, osteomyelitis)
- Infections of the abdominal cavity, including the minor pelvis, and diarrhoea of bacterial origin which requires antibiotic treatment
- Infections of the kidneys, urinary tract and genital organs, gonorrhoea.

Tarivid 200 film-coated tablets is also indicated for prevention of infection (including that caused by selective bowel decontamination) in patients with markedly lowered resistance to infection (e.g. in a neutropenic condition).

The following micro-organisms may be regarded as ofloxacin-sensitive.
Staphylococcus aureus, Staphylococcus epidermidis, Neisseria gonorrhoea, Neisseria meningitis, Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Hafnia, Proteus (indole-negative and indole-positive strains), Salmonella, Shigella, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas, Plesiomonas, Vibrio cholerae, Vibrio parahaemolyticus, Haemophilus influenzae, Chlamydia, Legionella.

**Moderately or variably sensitive:**
Enterococci, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus viridans, Serratia marcescens, Pseudomonas aeruginosa, Acinetobacter, Mycoplasma hominis, Mycoplasma pneumoniae, Mycobacterium tuberculosis, Mycobacterium fortuitum.

**Mainly insensitive to ofloxacin:**
Ureaplasma urealyticum, Nocardia asteroides, anaerobes (e.g. Bacteroides, Peptococcus, Peptostreptococcus, Eubacterium, Fusobacterium, Clostridium difficile).
Ofloxacin is not effective on Treponema pallidum.

**Single doses and daily dosages**
The following dosages are recommended:

<table>
<thead>
<tr>
<th>Indications</th>
<th>Single and daily doses</th>
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</thead>
<tbody>
<tr>
<td>Uncomplicated infections of the lower urinary tract</td>
<td>2 x 1/2 film-coated tablet Tarivid 200 per day</td>
</tr>
</tbody>
</table>
whole with plenty of liquid (1/2 to 1 glass). They can be taken on an empty stomach or with meals. Up to 400 mg ofloxacin can be given in a single dose. The daily dosage is generally divided into 2 equal doses (morning and evening). It is important to ensure that the intervals between doses are roughly equal.

The duration of treatment is determined by the response of the pathogens and the clinical picture. In principle it is advisable to continue the treatment for at least another three days after fever has subsided and the symptoms of illness have disappeared.

In most cases, treatment lasting 7 to 10 days is adequate for acute infections. The usual treatment period is 7 to 8 days for salmonellosis, 3 to 5 days for shigellosis and 3 days for intestinal infections caused by Escherichia coli.

For uncomplicated infections of the lower urinary tract, 3 days treatment with Tarivid 200 film-coated tablets is usually adequate.

For bone infections the treatment period is 3 to 4 weeks or longer in isolated cases.

If treating infections with beta-haemolytic streptococci (e.g. erysipelas) with proven sensitivity, treatment must last at least 10 days in order to prevent delayed damage such as rheumatic fever or glomerulonephritis. Since beta-haemolytic streptococci, however, vary in their sensitivity to ofloxacin, treatment of such infections requires proof of sensitivity in each individual case.

Until further experience has been gained, it is advisable not to exceed a treatment period of 2 months.

**Contraindications**

Tarivid 200 film-coated tablets must not be used in the following circumstances:
- Hypersensitivity to ofloxacin, other quinolones or one of the other ingredients (see under Composition).
- Epileptics and patients with a lowered convulsion threshold as a result of previous CNS damage, e.g. from cranio-cerebral injuries, inflammatory

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhoea</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
<tr>
<td>Infections of the kidneys, urinary tract and genital organs</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
<tr>
<td>Respiratory tract and ear, nose and throat infections</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
<tr>
<td>Bone infections</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
<tr>
<td>Infections of the abdominal cavity (incl. diarrhoea of bacterial origin)</td>
<td>2 x 1 film-coated tablet Tarivid 200 daily</td>
</tr>
</tbody>
</table>

In the individual case it may be necessary to increase the dose for pathogens with variable sensitivity, in severe infections (e.g. airways or bones) and if the patient’s response is poor. In these cases, the dosage can be increased to 2 x 2 film-coated tablets of Tarivid 200. The same applies with complicating accompanying factors.

For prophylaxis in patients with markedly lowered resistance to infection, the dose of 2 to 3 film-coated tablets of Tarivid 200 daily is recommended.

**Dosage in renal impairment**

Depending on the nature and severity of the disease, the first dose is the same as for patients with normal renal function. The maintenance dose should be reduced as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-20 ml/min</td>
<td>1/2 to 1 film-coated tablet every 24 hours</td>
</tr>
<tr>
<td>≤20 ml/min</td>
<td>1/2 film-coated tablet every 24 hours</td>
</tr>
<tr>
<td>Haemodialysis or peritoneal dialysis</td>
<td>Tablet every 24 hours</td>
</tr>
</tbody>
</table>

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

**Dosage in hepatic impairment**

The elimination of ofloxacin may be reduced in patients with severely impaired liver function (e.g. in cirrhosis with ascitis). It is therefore advisable to exceed a maximum daily dosage of 2 film-coated tablets of Tarivid 200 in such cases.

**Administration and duration of use**

Tarivid 200 film-coated tablets should be taken whole with plenty of liquid (1/2 to 1 glass). They can be taken on an empty stomach or with meals. Up to 400 mg ofloxacin can be given in a single dose. The daily dosage is generally divided into 2 equal doses (morning and evening). It is important to ensure that the intervals between doses are roughly equal.

The duration of treatment is determined by the response of the pathogens and the clinical picture. In principle it is advisable to continue the treatment for at least another three days after fever has subsided and the symptoms of illness have disappeared.

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**Contraindications**

Tarivid 200 film-coated tablets must not be used in the following circumstances:
- Hypersensitivity to ofloxacin, other quinolones or one of the other ingredients (see under Composition).
- Epileptics and patients with a lowered convulsion threshold as a result of previous CNS damage, e.g. from cranio-cerebral injuries, inflammatory
processes in the CNS or stroke (increased risk of cerebral convulsions),
- Patients who have experienced tendon disorders after taking quinolones.

Tarivid 200 film-coated tablets must not be used:
- In children and growing adolescents,
- During pregnancy,
- In breast-feeding mothers

Because, based on the results of animal studies, the risk of damage to joint cartilage in the growing body cannot be entirely ruled out.

**Interactions with other medicaments**

Concomitant use of antacids containing minerals or sucralfate can weaken the effect of Tarivid 200 film-coated tablets. The same applies to other medicines containing metallic ions (aluminium, iron, magnesium or zino). Therefore Tarivid 200 film-coated tablets must be taken about 2 hours before these drugs.

This is evidence that convulsions are more likely to occur if quinolones are taken at the same time as other medicines that lower the convulsion threshold. These include, for instance, some non-steroidal anti-inflammatory (fenbufen) or theophylline. The theophylline concentrations however are not appreciably altered by ofloxacin.

Especially during high-dose treatment, it is important to bear in mind that quinolones and other medicines excreted by tubular secretion (e.g. probenecid, cimetidine, frusemide, methotrexate) may impede each other’s elimination. This can lead to raised serum levels and a higher incidence of side-effects.

Quinolones, possibly including Tarivid 200 film-coated tablets, may potentiate the effect of coumarin derivatives. It is therefore advisable to monitor patients carefully who are concomitantly treated with coumarin drugs.

Tarivid 200 film-coated tablets can lead to a slight increase in the serum levels of glibenclamide. Since this makes hypoglycaemic episodes more likely, it is advisable to monitor blood glucose more closely in such cases.

**Influence on laboratory test**

Opiate or porphyrin analysis in urine can produce false-positive results during treatment with Tarivid 200 film-coated tablets.

**Warnings**

Very severe and/or persistent bouts of diarrhoea which occur during or in the first few weeks following treatment with various antibiotics (especially broad-spectrum antibiotics) may be evidence of bowel inflammation caused by Clostridium difficile, the most serious form of which is pseudomembranous colitis.

Diagnostic confirmation of this rare but potentially life-threatening disease is achieved by endoscopy and/or histology. Stool analysis for this pathogen and especially its cytotoxin is a reliable way of diagnosing a disease associated with Clostridium difficile.

If pseudomembranous colitis is suspected, the doctor must consider stopping treatment with Tarivid, depending on the indication, and starting suitable treatment (e.g. with teicoplanin orally) if appropriate. Medicine which inhibit peristalsis must not be used in such cases.

Inflammation of the tendons very rarely observed during quinolone treatment - mainly affecting the Achille Tendon - can lead to rupture of a tendon. Elderly patients are more likely to suffer tendinitis. Treatment with corticosteroids appears to favour rupture of tendons. If tendinitis is suspected, medical advice must be sought at once and the affected tendon treated appropriately, above all immobilised.

After consultation with the doctor, treatment with Tarivid should be discontinued, if need be. Also see «Contraindications» and «Side effects».

**Side effects**

**Effects on the gastro-intestinal tract**

Gastric disorders, abdominal pain, loss of appetite, nausea, vomiting or diarrhoea may occur during treatment with Tarivid 200 film-coated tablets.

As with antibiotics in general, diarrhoea may sometimes be a symptom of enterocolitis which in some cases may follow a haemorrhagic course. A particular form of enterocolitis associated with
antibiotic treatment is pseudomembranous colitis, in most cases caused by Clostridium difficile (see Warnings).

**Effects on liver and bile ducts**
Rarely liver enzymes may be elevated or liver function may be impaired with increased bilirubine levels. Very rarely cholestatic jaundice, hepatitis or severe liver damage may develop.

**Effects on the nervous system**
Headache, dizziness, sleep disturbances, restlessness and confusion may occur, very rarely drowsiness. Very rare side effects are tremor, unsteadiness of gait caused by disturbances of muscular coordination or extrapyramidal symptoms. Other very rare side effects are cerebral convulsions, paraesthesia and hypoaesthesia, visual disturbances (e.g. blurred vision, double vision, and altered colour vision), taste and smell disturbances (even loss of the sense of taste and smell) or balance problems. Tinnitus and hearing disturbances (even hearing loss in exceptional cases) are very rare with Tarivid 200 film-coated tablets. Very rarely there may be intensive dream experiences (even nightmares) and psychotic reactions such as state of agitation, anxiety, depressive moods and hallucinations. Certain psychotic reaction may lead to patients putting themselves at risk in many of these cases. Reactions of this kind can even happen after the first dose. Tarivid 200 film-coated tablets must be stopped immediately in such circumstances.

**Effects on the cardiovascular system**
After taking Tarivid 200 film-coated tablets, tachycardia and a transient fall in blood pressure may occur. A very rare side effect is collapse resulting from a sharp blood pressure decrease.

**Effects on the blood count**
Anaemia, leucopenia, agranulocytosis, thrombocytopenia or pancytopenia are very rare. This results from bone marrow depression in only a few cases. Very rarely haemolytic anaemia may develop.

**Effects on the kidneys**
Very rarely renal function may become impaired with increased serum creatinine, for instance; in isolated cases acute interstitial nephritis may occur. These reactions may progress to acute renal failure in some cases.

**Skin, mucosal, other reactions**
Skin and mucosal reactions may develop, e.g. pruritus, urticaria and skin rash (in exceptional cases with vesicles or pustules). Very rarely flush, erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis or vasculitis may arise. Vasculitis can generally take the form of petechiae, blistering and haemorrhages and small nodules with crust formation and, in exceptional cases may lead to skin lesions including necrosis. Vasculitis may also involve internal organs. Photosensitivity of the skin (e.g. symptoms similar to sunburn, nail discolouration or detachment) is a very rare side-effect. Patients treated with Tarivid 200 film-coated tablets should therefore avoid unnecessary exposure to sunlight and sources of UV light (sun lamps, sunbeds). Very rarely fever, eosinophilia or allergic pneumonitis may develop.

Very rarely, but even after the first dose of medication, anaphylactic or anaphylactoid reactions may occur, they may be manifest as stinging eyes, irritable cough and running nose, for example, but also as a blood pressure increase and angioedema of the skin and mucous membranes, e.g. of the face, tongue and larynx. In the worst cases, severe dyspnoea (even bronchospasm), a blood pressure decrease and/or shock may develop. In these cases treatment with Tarivid 200 film-coated tablets must be stopped at once. This type of reaction requires immediate medical treatment (e.g. treatment for shock, see “Emergency measures”).

Sweating may occur. Very rarely, muscle complaints such as pain or weakness may arise (particularly important in patients with myasthenia gravis, for instance). In isolated cases this may be evidence of rhabdomyolysis. Very rarely patients may experience joint and tendon symptoms (e.g. pain).

In very rare cases, treatment with quinolones may
The following measures can be recommended for a massive overdose in order to eliminate ofloxacin not yet absorbed, e.g. gastric lavage, administration of adsorbents and sodium sulphate (if possible, within the first 30 minutes) are recommended; antacids may be given to protect the gastric mucosa; diuretic therapy may also be carried out in order to promote elimination of the substance already absorbed.

c) Emergency measures for severe hypersensitivity reactions (shock)

In general, the following emergency measures are recommended:

At the first sign (e.g. skin reactions such as urticaria and flush, restlessness, headache, outbreaks of sweating, nausea) create a venous access.

As well as conventional emergency measures, elevate the legs, clear the airways and give oxygen!

Emergency medication:

- immediately: adrenaline i.v.

After diluting 1 ml of the 1:1000 proprietary adrenaline solution to produce 10 ml or by using a 1:10,000 adrenaline solution, first inject 1 ml of that (=0.1 mg adrenaline) slowly whilst monitoring pulse and blood pressure (watch for arrhythmias). The adrenaline dose can be repeated.

- followed by: volume replacement i.v.

  e.g. volume replacement agents (colloids), Ringer's lactate solution

- additionally: glucocorticoids i.v.

  e.g. 250 to 1000 mg methylprednisolone.

Glucocorticoid administration can be repeated.

The dosage figures relate to patients of normal weight; a weight-related adjustment is necessary for children.

Depending on the clinical symptoms, further therapeutic measures may be considered, e.g. artificial respiration, histamine antagonists. In the event of circulatory arrest, resuscitation according to the usual recommendations.

Pharmacological properties

Ofloxacin is a bactericidal quinolone antibiotic.
The principal mechanism of action of quinolones is the inhibition of bacterial DNA gyrase. This enzyme is required for DNA replication, transcription, repair and recombination. Its inhibition leads to the expansion and destabilisation of the DNA and ultimately to cell death of the micro-organisms. Some quinolones, including ofloxacin, may have a second mechanism of action unrelated to RNA which strengthens their bactericidal efficacy. The nature of this mechanism has not yet been explained.

See «Indications» on the sensitivity of bacteria.

**Toxicological properties**

**Acute toxicity**

The LD50 values after oral administration of ofloxacin are over 5,000 mg per kg bodyweight in the mouse, 3,590 mg per kg BW in the rat and between 500 and 1000 mg per kg BW in monkeys. The LD50 values after intravenous administration of ofloxacin are in the order of 210 mg per kg bodyweight in the mouse, 270 mg per kg BW in the rat.

**Subacute and chronic toxicity**

When testing the oral subacute toxicity of ofloxacin, 60 mg per kg bodyweight orally were tolerated by monkeys without any signs of systemic damage. Following a dosage of 180 mg per kg BW, two out of six monkeys suffered diarrhoea which proved fatal. In dogs, changes in the intestinal tract as well as liver and kidney damage occurred after 200 mg per kg bodyweight. Depending on the dogs’ age and ofloxacin dose, degenerative changes to joint cartilage were observed. Fourteen days’ treatment of adult dogs with 40 and 80 mg ofloxacin/kg BW did not cause any cartilage changes. Degenerative joint changes developed in 7-month-old dogs receiving doses of 50 and 200 mg per kg bodyweight. Three to 4-month-old dogs displayed cartilage lesions after 20 mg per kg bodyweight. Young dogs tolerated an ofloxacin dosage of 12.5 mg per kg BW without damage. Studies on subacute toxicity in rats and dogs were performed with intravenous ofloxacin. Cerebral convulsions occurred in rats after 200 mg ofloxacin per kg bodyweight, not after 20 and 63 mg per kg BW. Irrespective of the dose, morphological changes of the test were noted in animals which were still juveniles. However, testicular morphology in adult rats was unremarkable.

Dogs tolerated an i.v. dose of 4 mg per kg BW without any clinical symptoms. After 10 and 25 mg per kg BW, redness of the visible mucosa and swelling of the skin of the head appeared dose-dependently immediately after injection, which is indicative of histamine release. This is a phenomenon specific to dogs. There were no pathological organ findings, particularly no joint and testicular changes.

Chronic toxicity studies with oral ofloxacin in rats revealed increases in SGOT and alkaline phosphatase in serum as well as morphological changes of cartilage after 270 mg per kg BW. Cartilage changes similar to osteochondrosis were already noted with a dosage of 90 mg per kg BW. Ofloxacin doses of 10 and 30 mg per kg BW were tolerated by rats without any historical evidence of organ damage. Oral doses of 90 mg of ofloxacin per kg BW for 90 days and 40 mg per kg BW for one year were tolerated by monkeys, although isolated bouts of diarrhoea were observed. In specific studies ofloxacin was neither ototoxic nor nephrotoxic.

There is no evidence of any cataractogenic or co-cataractogenic effects.

**Reproduction, toxicology and mutagenicity**

Ofloxacin has no influence on fertility, perinatal or postnatal development and is not teratogenic. Several in vitro and in vivo test on the induction of gene and chromosomal mutations proved negative. No long-term animal studies on carcinogenicity have been carried out.

**Pharmacokinetics**

After oral administration to fasting volunteers, ofloxacin is absorbed rapidly and almost completely. The peak serum concentration after a single oral dose of 200 mg is 2.6 µg/ml on average and is reached within one hour. The serum elimination half-life is 5.7 to
7.0 hours and is not dose-dependent. The apparent distribution volume is 120 litres. Multiple dosing does not greatly increase the serum concentration (accumulation factor for twice daily administration: 1.5). Plasma protein binding is around 25%. Ofloxacin is less than 5% biotransformed. The two main metabolites recovered in urine are N-desmethyl-ofloxacin and ofloxacin-N-oxide. Elimination is mainly by the kidneys. 80% to 90% of the dose is recovered in the urine as unchanged substance. In bile ofloxacin is found in a glucuronated form. The pharmacokinetics of ofloxacin are very similar after intravenous infusion and oral administration. In patients with renal impairment, the serum half-life is lengthened; total and renal clearance of ofloxacin decrease in line with creatinine clearance.

**Bioavailability**
Tarivid 200 film-coated tablets are absorbed rapidly and almost completely after oral administration (bioavailability approx. 95%).

**Major incompatibilities**
Not applicable.

**Miscellaneous**
Patients who have reacted to other quinolones with severe side-effects (e.g. severe neurological reactions) have a greater risk of reacting to ofloxacin in a similar way.

Since ofloxacin is predominantly excreted via the kidneys, the dose must be adjusted for patients with impaired renal function.

**Special storage instructions**
None.

**Shelf life**
Tarivid 200 film-coated tablets are stable for 5 years.