APPROVED
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INSTRUCTION
for medical use

ATOVAX®

Composition:
active substance: moxifloxacin;
1 film-coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin;
excipients: microcrystalline cellulose, sodium starch glycolate (type A), povidone K 29/32, magnesium stearate, coating Opadry 03F84827 pink*;
*Opadry 03F84827 pink: hypromellose, titanium dioxide (E 171), iron oxide red (E 172), polyethylene glycol, talc.

Pharmaceutical form. Film-coated tablets.
Basic physico-chemical properties: film-coated, pink, capsule-shaped tablets smooth on both sides.

Pharmacotherapeutic group. Antimicrobial agents for systemic use. Quinolone group antibacterial agents. ATC code J01M A14.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
In vitro moxifloxacin is effective against many Gram-positive and Gram-negative microorganisms. The bactericidal action of moxifloxacin results from the inhibition of both types of II topoisomerases (DNA gyrase and topoisomerase IV), required for bacterial DNA replication, transcription and repair.
It is believed that the C8-methoxy residue contributes to activity and weakens the selection of resistant mutants of Gram-positive bacteria compared to the C8-H residue. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux associated with the norA or pmrA genes seen in certain Gram-positive bacteria.
Pharmacodynamic investigations indicate that moxifloxacin has a concentration-dependent bactericidal activity. Minimum bactericidal concentrations (MBC) usually correspond to the minimum inhibitory concentrations (MIC).
Effect on the intestinal flora in humans
The following changes in the intestinal flora were seen in two volunteer studies following oral administration of moxifloxacin. The number of *E.coli*, *Bacillus spp.*, *Enterococcus* and *Klebsiella spp*. was reduced, as well as that of anaerobes *Bacteroides vulgatus*, *Bifidobacterium spp.*, *Eubacterium* and *Peptostreptococcus*. An increase in the number of *Bacteroides fragilis* was observed. The number of the above-mentioned microorganisms returned to normal within two weeks.
Mechanism of resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not affect the antibacterial efficacy of moxifloxacin. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to moxifloxacin.
In vitro resistance to moxifloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.
Cross-resistance is observed with other fluoroquinolones. However, as moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.
Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2011)

Table 1

Microorganism	Susceptible	Resistant
Staphylococcus spp.	≤ 0,5 mg/l ≥ 24 mm	> 1 mg/l < 21 mm
S. pneumoniae	≤ 0,5 mg/l ≥ 22 mm	> 0,5 mg/l < 22 mm
Streptococcus groups A, B, C, G	≤ 0,5 mg/l ≥ 18 mm	> 1 mg/l < 15 mm
H. influenzae	≤ 0,5 mg/l ≥ 25 mm	> 0,5 mg/l < 25 mm
M. catarrhalis	≤ 0,5 mg/l ≥ 23 mm	> 0,5 mg/l < 23 mm
Enterobacteriaceae	≤ 0,5 mg/l ≥ 20 mm	> 1 mg/l < 17 mm
Non-species related breakpoints*	≤ 0,5 mg/l	> 1 mg/l
* Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined.		

Microbiological susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species of microorganisms. It is desirable to have access to the information on the local microorganism resistance, particularly when treating severe infections. If necessary, expert advice regarding antibiotic resistance should be sought where the local prevalence of resistance is so strong that the effect of the pharmaceutical product in at least some types of infectious pathogens is questionable.
Susceptible species
Aerobic Gram-positive microorganisms
Gardnerella vaginalis
*Staphylococcus aureus** (methicillin-susceptible)
Streptococcus agalactiae (Group B)
Streptococcus milleri group* (*S. anginosus*, *S. constellatus* and *S. intermedius*)
*Streptococcus pneumoniae**
*Streptococcus pyogenes** (Group A)
Streptococcus viridans group *(S. viridans*, *S. mutans*, *S. mitis*, *S. sanguinis*, *S. salivarius*, *S. thermophilus)*
Aerobic Gram-negative microorganisms
Acinetobacter baumanii

*Haemophilus influenzae**
*Haemophilus parainfluenzae**
Legionella pneumophila
*Moraxella (Branhamella) catarrhalis**
Anaerobic microorganisms
Fusobacterium spp.
Prevotella spp.
Other microorganisms
*Chlamydophila (Chlamydia) pneumoniae**
*Chlamydia trachomatis**
Coxiella burnetii
Mycoplasma genitalium
Mycoplasma hominis
*Mycoplasma pneumoniae**
Species that may acquire resistance
Aerobic Gram-positive microorganisms
*Enterococcus faecalis**
*Enterococcus faecium**
Staphylococcus aureus (methicillin-resistant)$^{+}$
Aerobic Gram-negative microorganisms
*Enterobacter cloacae**
*Escherichia coli**#
*Klebsiella pneumoniae**#
Klebsiella oxytoca
*Neisseria gonorrhoeae**+
*Proteus mirabilis**
Anaerobic microorganisms
*Bacteroides fragilis**
*Peptostreptococcus spp.**
Resistant species
Aerobic Gram-negative microorganisms
Pseudomonas aeruginosa

* Satisfactory activity has been demonstrated in susceptible strains in clinical studies in the approved clinical indications.

ESBL-producing strains are commonly resistant to fluoroquinolones.

+ Resistance rate > 50 % in one or more countries.

Pharmacokinetics.

Absorption and Bioavailability

Following oral administration moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91 %.

The pharmacokinetics is linear when using 50–800 mg single doses and 600 mg daily doses for 10 days. Steady state is reached within three days. Following a 400 mg oral dose peak blood concentration (C_{max}) is reached within 0.5–4 hours and is 3.1 mg/l. Peak and trough plasma concentrations at steady state (400 mg once daily) are 3.2 and 0.6 mg/l, respectively. At steady-state the exposure within the dosing interval is approximately 30 % higher than after the first dose.

Distribution

Moxifloxacin is distributed in extravascular spaces rapidly, after a dose of 400 mg, the area under the "concentration-time" curve (AUC) is 35 mcg/l. The steady-state volume of distribution is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed plasma protein binding of approximately 40–42% independent of the concentration of the drug. Moxifloxacin is mainly bound to blood plasma albumin.

Peak concentration (geometric mean) following administration of a single oral dose of 400 mg moxifloxacin

Table 2

Tissue	Concentration	Local level – blood plasma level
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75–1.3
Blister fluid	1.6[1] mg/l	1.7[1]
Bronchial mucosa	5.4 mg/kg	1.7–2.1
Alveolar macrophages	56.7 mg/kg	18.6–70.0
Epithelial lining fluid	20.7 mg/l	5–7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal polyps	9.1 mg/kg	2.6
Interstitial fluid	1.0[2] mg/l	0.8–1.4[2,3]
Female genital organs*	10.2[4] mg/kg	1.72[4]

* Intravenous administration of a single 400 mg dose.

[1] 10 hours after administration.

[2] Unbound concentration.

[3] From 3 up to 36 hours post dose.

[4] At the end of infusion.

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and fecal/biliary pathways unchanged as well as in the form of inactive metabolites: sulpho-compounds (M1) and glucuronides (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. In *in vitro* and clinical Phase I studies no metabolic pharmacokinetic interactions with other medicinal products undergoing Phase I biotransformation involving the cytochrome P450 enzyme system were observed. There is no indication of oxidative metabolism.

Elimination

The half-life of the drug is approximately 12 hours. The mean apparent total clearance following a 400 mg dose ranges from 179 to 246 ml/min. Renal clearance amounted to about 24–53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. After a 400 mg dose, urinary excretion (approximately 19 % for the unchanged drug, approximately 2.5 % for M1, and approximately 14 % for M2) and fecal excretion (approximately 25 % of the unchanged drug, approximately 36 % for M1, and no excretion for M2) totalled to approximately 96 %. Concomitant administration of ranitidine and probenecid does not change renal clearance of the parent drug.

Pharmacokinetics in different groups of patients.

Elderly patients and patients with low body weight

Higher plasma concentrations of the drug are observed in healthy volunteers with low body weight (women in particular) and in healthy elderly volunteers.

Renal impairment

No significant changes in the pharmacokinetics of moxifloxacin are found in patients with renal impairment (including patients with creatinine clearance > 20 ml/min/1.73 m^2). As renal function decreases, concentration of the M2 metabolite (glucuronide) increases by up to a factor of 2.5 (in patients with creatinine clearance < 30 ml/min/1.73 m^2).

Hepatic impairment

On the basis of the pharmacokinetic studies carried out in patients with liver failure (Child-Pugh classes A–C), it is not possible to determine whether there is any difference compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas

exposure to the parent drug was comparable to exposure in healthy volunteers. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

Clinical particulars.

Indications.

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section "Administration details" and "Adverse reactions") moxifloxacin must only be prescribed when the use of other antibiotics is inappropriate. This applies to all indications listed below.

Situations where other antibiotics are considered inappropriate are where:

• there is resistance to other first-line antibiotics recommended for the infection;
• other first-line antibiotics are contraindicated in an individual patient;
• other first-line antibiotics have caused adverse reactions requiring treatment to be stopped;
• treatment with other first-line antibiotics has failed.

Treatment of the following bacterial infections caused by microorganisms susceptible to moxifloxacin (see sections "Pharmacological properties", "Administration details" and "Adverse reactions") in patients aged 18 years and older.

- Acute bacterial sinusitis.
- Exacerbation of chronic obstructive pulmonary disease including bronchitis.
- Community-acquired pneumonia, except severe community-acquired pneumonia.
- Mild to moderate pelvic inflammatory diseases (including infections of the female upper reproductive tract, including salpingitis and endometritis), not associated with tubo-ovarian or pelvic abscess.

Moxifloxacin in tablet form is not recommended for use as monotherapy of mild to moderate pelvic inflammatory disease but may be used in combination with other appropriate antibacterial agents (e.g. cephalosporins) due to increasing moxifloxacin resistance of *Neisseria gonorrhoeae*, unless moxifloxacin-resistant Neisseria gonorrhoeae can be excluded (see sections "Pharmacological properties" and "Administration details").

Moxifloxacin in tablet form may also be used to complete a course of treatment in which the initial treatment with moxifloxacin in parenteral form was effective and was prescribed for the following indications:

- community-acquired pneumonia;
- complicated skin and skin structure infections.

It is not recommended to use moxifloxacin in tablet form to initiate treatment for any type of skin and skin structure infection or in case of severe community-acquired pneumonia.

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

Contraindications.

- Hypersensitivity to moxifloxacin or other quinolones or to any of the drug excipients.
- Pregnancy or breastfeeding (see section "Use during pregnancy or breastfeeding").
- Age less than 18 years.
- Patients with a history of tendon disease related to quinolone treatment.

Both in preclinical and clinical studies, changes in cardiac electrophysiology have been observed, in the form of QT prolongation after administration of moxifloxacin. For safety reasons, the drug is therefore contraindicated in patients with:

- congenital or diagnosed acquired QT interval prolongation;
- electrolyte disturbances, particularly in uncorrected hypokalemia;
- clinically relevant bradycardia;
- clinically relevant heart failure with reduced left-ventricular ejection fraction;
- a history of symptomatic arrhythmias.

The drug should not be used concurrently with other medicinal products that prolong the QT interval (see section "Interaction with other medicinal products and other forms of interaction"). Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child-Pugh class C) and in patients with increased transaminase levels (5-fold above ULN).

Interaction with other medicinal products and other forms of interaction.

Interaction with medicinal products

Medicinal products that can prolong the QT interval

An additive effect of moxifloxacin and other medicinal products that may prolong the QT interval cannot be excluded. This interaction increases the risk of ventricular arrhythmias, including pirouette-type ventricular tachycardia *(torsade de pointes).* Therefore, co-administration of moxifloxacin with any of the following medicinal products is contraindicated (see also section "Contraindications"):

- class IA antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide);
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide);
- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride);
- tricyclic antidepressants;
- certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin for intravenous administration, pentamidine, antimalarials, in particular halofantrine);
- certain antihistamines (terfenadine, astemizole, mizolastine);
- others (cisapride, vincamine IV, bepridil, diphemanil).

Potassium-lowering medicinal products

Moxifloxacin should be used with caution in patients taking drugs that can reduce potassium levels (e.g. loop and thiazide-type diuretics, enemas and laxatives (high doses), corticosteroids, amphotericin B) or drugs associated with clinically significant bradycardia.

Drugs containing bivalent or trivalent cations

An interval of about 6 hours should be left between administration of agents containing bivalent or trivalent cations (e.g. antacids containing magnesium or aluminium, didanosine tablets, sucralfate and agents containing iron or zinc) and administration of moxifloxacin.

Activated charcoal

Concomitant administration of activated charcoal and a 400 mg oral dose of moxifloxacin leads to a reduction of systemic bioavailability of the product by more than 80 % due to the inhibition of its absorption. Therefore, the concomitant use of these two medicinal products is not recommended (except for overdose cases, see also section "Overdose").

Digoxin

An increase of C_{max} of digoxin by approximately 30 % at steady state without affecting the AUC or trough levels was observed in healthy volunteers after repeated administration of moxifloxacin. Therefore, no precautionary measures are required for concurrent use with digoxin.

Glibenclamide

In studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of glibenclamide concentration at the peak level by approximately 21 %. The combination of glibenclamide and moxifloxacin could theoretically result in a mild and transient hyperglycemia. However, the observed pharmacokinetic changes did not result in changes of the pharmacodynamic parameters (blood glucose level, insulin level). Therefore, no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

Change in the International Normalized Ratio (INR) value

Numerous cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulant agents concomitantly with antibacterial products, including fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. Infectious diseases (and the concomitant inflammation), old age and general condition of the patient are risk factors. These

circumstances make it difficult to evaluate whether the INR deviation is caused by the infection or the treatment. More frequent monitoring of the INR may be appropriate. If necessary, appropriate dose adjustment for the oral anticoagulant should be performed.
The following substances have been proved to have no clinically relevant interaction with moxifloxacin: ranitidine, calcium supplements, theophylline, oral contraceptives, cyclosporine, itraconazole, morphine administered parenterally, probenecid. *In vitro* studies of human cytochrome P450 enzymes support these findings. Therefore, a metabolic interaction via cytochrome P450 enzymes is unlikely.
Interaction with food
No clinically relevant interaction with food, including dairy products, has been identified for moxifloxacin.

Administration details.
The use of moxifloxacin should be avoided in patients who have a history of serious adverse reactions as a result of using medicinal products containing quinolones or fluoroquinolones (see section "Adverse reactions"). Treatment of such patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section "Contraindications").
The benefits of moxifloxacin treatment, especially in infections with a low degree of severity, should be evaluated considering the information contained in this section.
QT_c interval prolongation and clinical conditions potentially related to QT_c interval prolongation
In some patients, the use of moxifloxacin may lead to the prolongation of the QT interval on the electrocardiogram (ECG). The analysis of ECG results has shown that the prolongation of the QT_c interval when using moxifloxacin was 6 msec ± 26 msec (1.4 % compared to baseline). As women, compared with men, tend to exhibit a longer QT interval, they may be more sensitive to products that prolong the QT interval. Elderly patients may also be more susceptible to the effects on the QT interval associated with the product.
Medicinal products that can lower potassium levels should be used with caution in patients receiving moxifloxacin (see sections "Contraindications" and "Interaction with other medicinal products and other forms of interaction").
Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially in elderly patients and young women), such as acute myocardial ischemia or QT interval prolongation, as this increases the risk of ventricular arrhythmias, including pirouette-type ventricular tachycardia *(torsade de pointes*), and cardiac arrest (see section "Contraindications").
The extent of QT interval prolongation may increase as concentrations of the medicinal product increase. Therefore, the recommended dose should not be exceeded.
Treatment should be discontinued, and an ECG performed if signs of arrhythmia occur during treatment with the product.
Hypersensitivity/allergic reactions
Hypersensitivity and allergic reactions after the first administration of fluoroquinolones, including moxifloxacin, have been reported. Anaphylactic reactions may take the form of a life-threatening shock even after the first administration of the product. In cases of clinical manifestation of severe hypersensitivity reactions the use of moxifloxacin should be discontinued and appropriate therapy (for example, treatment for shock) should be initiated.
Severe liver disorders
Cases of fulminant hepatitis potentially leading to liver failure, including fatal cases, have been reported with moxifloxacin (see section "Adverse reactions"). Patients are advised to contact their physician before continuing treatment if signs and symptoms of fulminant hepatitis develop, such as rapidly developing asthenia accompanied by jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
Liver functions should be investigated if liver dysfunction symptoms occur.
Severe cutaneous adverse reactions

Severe cutaneous adverse reactions have been reported with moxifloxacin, including toxic epidermal necrolysis (TEN, also known as Lyell's syndrome), Stevens–Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS), which may be life-threatening or lethal (see sections "Adverse reactions"). Patients should be informed of the signs and symptoms and the need for close monitoring for severe adverse skin reactions when having the drug prescribed. If any signs or symptoms indicating these reactions emerge, moxifloxacin should be discontinued immediately, and alternative treatment should be considered. If a patient develops such severe reactions as SJS, TEN, AGEP or DRESS when using moxifloxacin, under no circumstances should moxifloxacin treatment be resumed.

Patients predisposed to seizures

Quinolones are known to cause seizures. Moxifloxacin should be used with caution in patients with central nervous system (CNS) disorders or other risk factors that can trigger seizures or lower the seizure threshold. If seizures occur, the use of moxiflocaxin should be stopped and appropriate measures taken.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse 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. There are no effective pharmacological methods of treatment of the symptoms of long lasting or disabling adverse reactions associated with fluoroquinolones. Moxifloxacin 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, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy leading to paresthesia, hypesthesia, dysesthesia or weakness, have been reported in patients receiving quinolones or fluoroquinolones. Patients taking moxifloxacin are advised to inform their physician about the development of the following symptoms of neuropathy: pain, burning, tingling, numbness or weakness, before continuing the treatment in order to prevent the development of potentially irreversible conditions, (see section "Adverse reactions").

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In rare cases, depression or psychotic reactions have led to the development of suicidal thoughts and self-injurious behavior, in particular suicide attempts (see section "Adverse reactions"). If the patient develops such reactions, moxifloxacin should be discontinued, and appropriate measures taken. Caution should be exercised when prescribing moxifloxacin in patients with psychiatric disorders or a history of psychiatric disorders.

Antibiotic-associated diarrhea, including colitis

The use of broad-spectrum antibiotics including moxifloxacin has been reported to cause antibiotic-associated diarrhea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and diarrhea associated with *Clostridium difficile*, which may range in severity from mild diarrhea to fatal colitis. Therefore, it is important to consider the possibility of this diagnosis in patients who develop serious diarrhea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate sanitary and epidemiological measures should be undertaken with the aim of reducing the risk of infection transmission. Medicinal products that inhibit peristalsis are contraindicated in patients who develop serious diarrhea.

Patients with myasthenia gravis

Moxifloxacin should be used with caution in patients with myasthenia gravis because of a possible exacerbation of symptoms.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to the Achilles tendon), sometimes bilateral, may occur within 48 hours of starting treatment with quinolones and fluoroquinolones, or even several months after the discontinuation of treatment (see sections "Contraindications" and "Adverse reactions"). Elderly patients or patients with renal impairment, or with solid organ transplants, as well as those treated with corticosteroids, have a higher risk of developing tendinitis and tendon rupture. Therefore, concurrent use of corticosteroids with moxifloxacin should be avoided.

At the first signs of tendinitis (e.g. inflammation and swelling accompanied by pain) treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be treated appropriately (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Aortic aneurysm/dissection, heart valve regurgitation / insufficiency.

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after administration of fluoroquinolones.

Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal cases), and of regurgitation / insufficiency of any of the heart valves have been reported in patients receiving fluoroquinolones (see section "Adverse reactions").

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with history of aortic aneurysm or congenital heart valve disease, or in patients diagnosed with aortic aneurysm and/or aortic dissection or heart valve disease, or in the presence of other risk factors or conditions predisposing:

- for both aortic aneurysm/dissection and heart valve regurgitation/insufficiency (e.g. connective tissue disorders such as Marfan syndrome or vascular Ehlers–Danlos syndrome, Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis);
- for aortic aneurysm/dissection (e.g. vascular disorders such as Takayasu's arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome);
- for heart valve regurgitation/insufficiency (e.g. infective endocarditis).

The risk of aortic aneurysm/dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

Patients should seek immediate medical attention in case of sharp abdominal, chest or back pain.

Patients should be recommended to seek immediate medical attention in case of acute dyspnea, new onset of heart palpitations, or development of edema of the abdomen or lower extremities.

Patients with renal impairment

Moxifloxacin should be used with caution in elderly patients with renal disorders if they are unable to maintain adequate fluid intake, because dehydration increases the risk of renal failure.

Vision disorders

If vision deterioration or any other effects on the eyes are experienced, an ophthalmologist should be consulted immediately (see sections "Effect on reaction rate when driving motor transport or using other mechanisms" and "Contraindications").

Dysglycemia

As with all fluoroquinolones, deviations of blood glucose from normal levels, including both hypoglycemia and hyperglycemia, have been reported with moxifloxacin (see section "Adverse reactions"). In moxifloxacin-treated patients, dysglycemia occurred predominantly in elderly patients with diabetes mellitus receiving concomitant treatment with oral hypoglycemic agents (e.g. sulfonylurea) or with insulin.

Cases of hypoglycemic coma have been recorded. Patients with diabetes mellitus are advised to monitor their blood glucose levels carefully (see section "Adverse reactions").

Prevention of photosensitivity reactions

The use of quinolones has been reported to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk of inducing photosensitivity. Nevertheless, patients should be advised to avoid exposure to UV radiation and extensive and/or intensive sunlight during treatment with moxifloxacin (see section "Adverse reactions").

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with insufficient glucose-6-phosphate dehydrogenase activity (diagnosed or in the family history) are prone to hemolytic reactions when treated with quinolones. Therefore, such patients should use moxifloxacin with caution.

Patients with pelvic inflammatory disease

For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian abscess or pelvic abscess), for whom intravenous treatment is considered necessary, treatment with moxifloxacin in tablet form is not recommended.

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant bacteria *Neisseria gonorrhoeae*. Therefore, in such cases moxifloxacin should be empirically co-administered with another appropriate antibiotic (e.g. cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Patients with specific complicated infections of the skin and subcutaneous tissue

Clinical efficacy of intravenous administration of moxifloxacin in the treatment of severe infections associated with burns, fasciitis and diabetic foot infection accompanied by osteomyelitis has not been established.

Interference with biological tests

Moxifloxacin therapy may interfere with the *Mycobacterium spp.* culture test due to suppression of microbial growth, which, on its part, may result in false-negative results in samples taken from patients currently receiving moxifloxacin.

Patients with infections caused by methicillin-resistant Staphylococcus aureus (MRSA)

Moxifloxacin is not recommended for the treatment of infections caused by MRSA. In case of a suspected or confirmed infection caused by MRSA, treatment with an appropriate antibacterial agent should be initiated (see section "Pharmacological properties").

Children

Moxifloxacin has adverse effects on the cartilage in juvenile animals, therefore the use of moxifloxacin in children (under the age of 18) is contraindicated (see section "Contraindications").

Information about excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per one coated tablet, i.e,. is essentially sodium-free.

Use during pregnancy or breastfeeding.

Pregnancy

The safety of moxifloxacin use during pregnancy has not been determined. The results of animal studies indicate reproductive toxicity. The potential risk for humans is unknown.

Due to the discovered risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals (according to experimental data) and cases of reversible joint injuries described in children receiving some fluoroquinolones, moxifloxacin is contraindicated in pregnant women (see section "Contraindications").

Breastfeeding

There is no data available as to the use of the product in breastfeeding women. The results of preclinical studies indicate that small amounts of moxifloxacin can be secreted in breastmilk.

Considering the absence of data as to humans and the availability of experimental data as to the risk of damage to the weight-bearing cartilage of immature animals, breastfeeding is contraindicated during moxifloxacin therapy (see section "Contraindications").

Fertility

Animal studies do not indicate impairment of fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.
No studies on the effects of moxifloxacin on the ability to drive motor transport and use other mechanisms have been performed. However, fluoroquinolones including moxifloxacin may impair the ability to drive motor transport or use other mechanisms due to CNS reactions such as dizziness, acute temporary loss of vision or acute and short-term loss of consciousness, syncope (see section "Adverse reactions"). Patients should be advised to monitor their reaction to moxifloxacin before driving motor transport or using other mechanisms.

Dosage and administration.
Adults
It is recommended to take 1 tablet (400 mg) of moxifloxacin once a day.
The tablets are to be swallowed whole with a sufficient amount of water. The medicinal product may be taken without regard to meals.
Duration of treatment
The duration of treatment with moxifloxacin tablets depends on the type of infection and is as follows:
- exacerbation of chronic obstructive pulmonary disease, including bronchitis – 5–10 days;
- community-acquired pneumonia – 10 days;
- acute bacterial sinusitis – 7 days;
- mild to moderate pelvic inflammatory disease – 14 days.

According to clinical trials, the duration of treatment with moxifloxacin tablets is up to 14 days.
Sequential (intravenous/oral) therapy
In studies with sequential therapy most patients switched from intravenous to oral moxifloxacin within 4 days (community-acquired pneumonia) or 6 days (complicated infections of the skin and subcutaneous tissue). The recommended total duration of intravenous and oral treatment with moxifloxacin is 7–14 days for community-acquired pneumonia and 7–21 days for complicated infections of the skin and subcutaneous tissue.
It is not recommended to exceed the indicated dose (400 mg once a day) and duration of therapy for any indication being treated.
Renal / hepatic impairment
No dose adjustment is required in patients with mild to moderate renal impairment as well as in patients on chronic hemodialysis and continuous ambulatory peritoneal dialysis (see section "Pharmacological properties").
There is no credible information regarding patients with impaired hepatic function (also see section "Contraindications").
Elderly patients/patients with low bodyweight
No dose adjustment is required in elderly patients / patients with a low bodyweight.

Children.
Moxifloxacin is contraindicated in children (under the age of 18). The efficacy and safety of using moxifloxacin in children have not been established (also see section "Contraindications").

Overdose.
No specific countermeasures after accidental overdose are required. In the event of overdose, symptomatic treatment based on the clinical picture should be implemented and ECG monitoring should be undertaken, due to the possibility of QT interval prolongation.
Concomitant administration of activated charcoal with a 400 mg oral dose of moxifloxacin will reduce systemic availability of the medicinal product by more than 80 %. The use of activated charcoal during the early stage of absorption may be useful to prevent an increase in the systemic effect of moxifloxacin in cases of oral overdose.

Adverse reactions.
The following adverse reactions were observed in clinical trials following administration of moxifloxacin at a dose of 400 mg per day (only intravenous therapy, sequential [intravenous / oral] and oral) and during the post-marketing period. Adverse reactions are classified according to their frequency.
Apart from nausea and diarrhea all adverse reactions were observed at frequencies below 3 %. Within each frequency grouping, adverse reactions are listed in order of decreasing seriousness. The frequencies are defined as follows: common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000, including individual cases), not known (frequency cannot be estimated from the available data).

Table 3

System Organ Classes (MedDRA)	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Superinfection due to resistant bacteria or fungi, e.g. oral or vaginal candidiasis				
Blood and lymphatic system disorders		Anemia, leucopenia(s), neutropenia, thrombocytopenia, trombocythemia, eosinophilia, prolongation of prothrombin time/increase of INR		Prothrombin level increased/INR decreased, agranulocytosis, pancytopenia	
Immune system disorders		Allergic reactions (see section "Administration details")	Anaphylaxis including rare cases of shock (life threatening), allergic edema/angioedema including laryngeal edema (potentially life threatening) (see section "Administration details")		

Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolic and nutritional disorders		Hyperlipidemia	Hyperglycemia, hyperuricemia	Hypoglycemia, hypoglycemic coma	
*Psychiatric disorders**		Anxiety reactions, psychomotor hyperactivity/agitation	Emotional lability, depression (in very rare cases with possible self-injurious behavior, such as suicidal ideations/thoughts, or suicide attempts (see section "Administration details")), hallucinations, delirium	Depersonalization, psychotic reactions (with possible self-injurious behavior, such as suicidal ideations/thoughts, or suicide attempts (see section "Administration details"))	
*Nervous system**	Headache, dizziness	Paresthesia/dysesthesia, taste disorders (including ageusia in very rare cases), confusion and disorientation, sleep disorders (predominantly insomnia), tremor, vertigo, somnolence	Hypoesthesia, smell disorders (including anosmia), abnormal dreams, disturbed coordination (including gait abnormalities due to dizziness or vertigo), seizures of various clinical manifestations (including *grand mal* seizures (see section	Hyperesthesia	

			"Administration details")), disturbed attention, speech disorders, amnesia, peripheral neuropathy and polyneuropathy		
*Organs of vision**		Visual disturbances, including diplopia and blurred vision (especially in the course of CNS reactions (see section "Administration details"))	Photophobia	Transient loss of vision (especially in the course of CNS reactions (see section "Administration details" and "Effect on reaction rate when driving motor transport or using other mechanisms")), uveitis, bilateral acute iris transillumination (see section "Administration details").	
*Organs of hearing and vestibular apparatus**			Tinnitus, hearing impairment, including deafness (usually reversible)		
*Cardiovascular disorders***	QT interval prolongation in patients with hypokalemia (see section "Administration details" and "Contraindications")	QT interval prolongation (see section "Administration details"), palpitations, tachycardia, atrial fibrillation, angina	Ventricular tachyarrhythmias, syncope (i.e. acute and short-term loss of consciousness), arterial hypertension, arterial hypotension	Unspecified arrhythmias, "pirouette-type" ventricular tachycardia (*torsade de pointes* (see section "Administration details")),	

		pectoris, vasodilation		cardiac arrest (see section "Administration details"), vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)			
Digestive system	Nausea, vomiting, abdominal pains, diarrhea	Decreased appetite and food intake, constipation, dyspepsia, flatulence, gastritis, increased amylase	Dysphagia, stomatitis, antibiotic-associated colitis (including pseudomembranous colitis, in very rare cases associated with life-threatening complications (see section "Administration details"))		
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (including LDH increase (Lactate dehydrogenase)), increased bilirubin, increased GGTP (gamma-glutamyl transpeptidase), increase in blood alkaline phosphatase	Jaundice, hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases (see section "Administration details"))	
Skin and subcutaneous tissue		Pruritus, rash, urticaria, dry skin		Bullous skin reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis (potentially life-	Acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) (see

				threatening (see section "Administration details"))	section "Administration details"), fixed drug eruption, photosensitivity reactions (see section "Administration details")
*Musculoskeletal system**		Arthralgia, myalgia	Tendinitis (see section "Administration details"), tendon rupture (see section "Administration details"), muscle twitching, muscle cramp, muscle weakness	Arthritis, muscle rigidity, exacerbation of symptoms of *myasthenia gravis* (see section "Administration details")	Rhabdomyolysis
Kidneys and urinary tract		Dehydration	Renal impairment (including increase in blood urea nitrogen and plasma creatinine), renal failure (see section "Administration details")		
*General disorders**		General weakness (predominantly asthenia or fatigue), painful conditions (including lower back, chest, limb pain, pelvic pain), hyperhidrosis	Edema		

Very rare cases of the following adverse reactions have been reported after treatment with other fluoroquinolones, which may possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including idiopathic intracranial hypertension), hypernatremia, hypercalcemia, hemolytic anemia, rhabdomyolysis.

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious adverse reactions affecting different, sometimes multiple, organ systems or sensory organs (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait abnormalities, neuropathy associated with paresthesia, fatigue, psychiatric symptoms, memory impairment, sleep disorders, impairment of hearing, vision, taste and smell) have been reported in patients receiving quinolones and fluoroquinolones, in some cases irrespective of the existing risk factors (see section "Administration details"). A range of psychiatric symptoms may occur as part of these adverse reactions, and may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling adverse reactions associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1000 and 1/10000 (corresponding to the "rare" frequency category).
**Cases of aneurysm and aortic dissection, sometimes complicated by rupture (including fatal cases), and regurgitation/insufficiency of any of the heart valves in patients receiving fluoroquinolones have been reported (see section "Administration details").

Reporting of adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
5 tablets are in a blister. 1 blister is in a carton box.
7 tablets are in a blister. 1 blister is in a carton box.
10 tablets are in a blister. 1 or 10 blisters are in a carton box.

Conditions of supply.
Prescription only.

Manufacturer.
LLC "KUSUM PHARM".

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

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