

FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY

MOXIMAC 400 MG TABLETS (MOXIFLOXACIN TABLET)

COMPOSITION:

Each film coated tablet contains:

Moxifloxacin Hydrochloride Ph. Eur Equivalent to Moxifloxacin 400 mg

DESCRIPTION

Moxifloxacin hydrochloride is a synthetic broad spectrum antibacterial agent. Chemically, Moxifloxacin is 1-cyclopropyl-7-[(S,S)2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid. Its molecular formula is $C_{21}H_{24}FN_3O_4 \cdot HCl$, and molecular weight is 437.9.

PHARMACOLOGICAL CLASSIFICATION

Fluoroquinolones

PHARMACEUTICAL FORM

Brick red colored, capsule shaped, biconvex, film coated tablets with plain surface on both the sides

PHARMACOLOGICAL ACTION

Pharmacokinetics

Absorption and Bioavailability

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

Pharmacokinetics is linear in the range of 50 - 800 mg single dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 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 to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 m·gh/l is observed. The steady-state volume of distribution (V_{ss}) is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

The following peak concentrations (geometric mean) were observed following administration of a single oral dose of 400 mg moxifloxacin:

Tissue	Concentration	Site: Plasma ratio
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 tract*	10.2 ⁴ mg/kg	1.72 ⁴

*intravenous administration of a single 400 mg dose

¹ 10 h after administration

² unbound concentration

³ from 3 h up to 36 h post dose

⁴ at the end of infusion

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

Elimination

Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body 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, recovery from urine (approximately 19% for unchanged drug, approximately 2.5% for M1, and approximately 14% for M2) and faeces (approximately 25% of unchanged drug, approximately 36% for M1, and no recovery for M2) totalled to approximately 96%.

Elderly and patients with low body weight

Higher plasma concentrations are observed in healthy volunteers with low body weight (such as women) and in elderly volunteers.

Renal impairment

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 m²). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m²).

Hepatic impairment

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

Pharmacodynamics

Mechanism of Action:

ATC code: J01MA14

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative pathogens.

The bactericidal action of moxifloxacin results from the inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription and repair. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. 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 have demonstrated that moxifloxacin exhibits a concentration dependent killing rate. Minimum bactericidal concentrations (MBC) were found to be in the range of the minimum inhibitory concentrations (MIC).

Effect on the intestinal flora in humans

The following changes in the intestinal flora were seen in volunteers following oral administration of moxifloxacin: *Escherichia coli*, *Bacillus* spp., *Enterococcus* spp., and *Klebsiella* spp. were reduced, as were the anaerobes *Bacteroides vulgatus*, *Bifidobacterium* spp., *Eubacterium* spp., and *Peptostreptococcus* spp. For *Bacteroides fragilis* there was an increase. These changes returned to normal within two weeks.

Mechanism of resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also effect 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.

Microbiological Susceptibility

<u>Commonly susceptible species</u>
<u>Aerobic Gram-positive micro-organisms</u> <i>Gardnerella vaginalis</i> <i>Staphylococcus aureus</i> * (methicillin-susceptible) <i>Streptococcus agalactiae</i> (Group B) <i>Streptococcus milleri</i> group* (<i>S. anginosus</i> , <i>S. constellatus</i> and <i>S. intermedius</i>) <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> * (Group A) <i>Streptococcus viridans</i> group (<i>S. viridans</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>S. sanguinis</i> , <i>S. salivarius</i> , <i>S. thermophilus</i>)
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> <i>Haemophilus influenzae</i> * <i>Haemophilus parainfluenzae</i> * <i>Legionella pneumophila</i> <i>Moraxella (Branhamella) catarrhalis</i> *

<u>Anaerobic micro-organisms</u> <i>Fusobacterium</i> spp. <i>Prevotella</i> spp.
<u>“Other” micro-organisms</u> <i>Chlamydophila (Chlamydia) pneumoniae</i> * <i>Chlamydia trachomatis</i> * <i>Coxiella burnetii</i> <i>Mycoplasma genitalium</i> <i>Mycoplasma hominis</i> <i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> * <i>Enterococcus faecium</i> * <i>Staphylococcus aureus</i> (methicillin-resistant) ⁺
<u>Aerobic Gram-negative micro-organisms</u> <i>Enterobacter cloacae</i> * <i>Escherichia coli</i> * <i>Klebsiella pneumoniae</i> *# <i>Klebsiella oxytoca</i> <i>Neisseria gonorrhoeae</i> * ⁺ <i>Proteus mirabilis</i> *
<u>Anaerobic micro-organisms</u> <i>Bacteroides fragilis</i> * <i>Peptostreptococcus</i> spp.*
Inherently resistant organisms
<u>Aerobic Gram-negative micro-organisms</u> <i>Pseudomonas aeruginosa</i>
*Activity has been satisfactorily 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

INDICATIONS

MOXIMAC 400mg Tablets are indicated for the treatment of adults (> 18 years of age) with the following bacterial infections caused by susceptible strains:

- Acute sinusitis
- Acute exacerbations of chronic bronchitis*
- Community acquired pneumonia.

-Mild to moderately severe inflammatory pelvic diseases (i.e. Infections of the upper female genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

Moximac 400mg Tablets are not recommended for monotherapy of mild to moderately severe inflammatory pelvic diseases. Preferably, they should be administered in combination with another suited antibiotic (such as

cephalosporin), due to the increasing resistance of *Neisseria gonorrhoeae* to moxifloxacin; that is, unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be ruled out.

-Complicated skin and skin structure infections.

-Complicated intra-abdominal infections including polymicrobial infections such as abscesses.

*MOXIMAC 400mg Tablets should only be used:

-When *Pseudomonas* is considered AND the patient is allergic to antipseudomonal penicillins/ cephalosporins;

-For resistant organisms with no other alternative antibiotics available

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

DOSAGE AND ADMINISTRATION

Dose (adults)

The recommended dose for MOXIMAC Tablet is 400 mg once daily (1 film-coated tablet) for the above mentioned indications and should not be exceeded.

Duration of treatment

The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations for the treatment of upper and lower respiratory tract infections are made:

Film-coated tablet:

Bronchitis: acute exacerbation of chronic bronchitis, 5 days *Pneumonia*: community acquired pneumonia, 10 days

Sinusitis: acute sinusitis, 7 days

Mild to moderately severe inflammatory pelvic diseases: 14 days

Complicated skin and skin structure infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 7 – 21 days

Complicated intraabdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy): 5 – 14 days

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to MOXIMAC. Therapy with MOXIMAC may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MOXIMAC and other antibacterial drugs, MOXIMAC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Method of administration

Film-coated tablet:

The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Geriatric patients

No adjustment of dosage is required in the elderly.

Children and adolescents

Efficacy and safety of MOXIMAC in children and adolescents have not been established.

Ethnic differences

No adjustment of dosage is required in ethnic groups.

Patients with hepatic impairment

No dosage adjustment is required in patients with impaired liver function.

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (including creatinine clearance $< 30 \text{ mL/min/1.73m}^2$) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis

CONTRAINDICATIONS

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- Pregnancy and lactation.
- Patients below 18 years of age.
- Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:

- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Moxifloxacin should not be used concurrently with other drugs that prolong the QT interval.

Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5 fold ULN.

DRUG INTERACTIONS

Antacids, Sucralfate, Multivitamins and Other Products Containing Multivalent Cations

Fluoroquinolones, including Moxifloxacin, form chelates with alkaline earth and transition metal cations. Oral administration of Moxifloxacin with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as didanosine buffered tablets for oral suspension or the pediatric powder for oral solution, may substantially interfere with the absorption of Moxifloxacin, resulting in systemic concentrations considerably lower than desired. 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.

Warfarin

Fluoroquinolones, including Moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age,

and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if Moxifloxacin is administered concomitantly with warfarin or its derivatives.

Changes in INR: A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibacterial agents, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Under these circumstances, it is difficult to evaluate whether the infection or the treatment caused the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Digoxin: After repeated dosing, moxifloxacin increased C_{max} of digoxin by approximately 30% without affecting AUC or trough levels. No precaution is required for use with digoxin.

Charcoal: Concomitant administration of charcoal with an oral dose of 400 mg moxifloxacin led to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases).

Interaction with food: Moxifloxacin has no clinically relevant interaction with food including dairy products.

Interactions With Medicinal Products

An additive effect on QT interval prolongation of moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore, co-administration of moxifloxacin with any of the following medicinal products is contraindicated:

- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

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

Concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of glibenclamide. The combination of glibenclamide and moxifloxacin could theoretically result in a mild and transient hyperglycaemia. However, the observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

It has shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.

ADVERSE REACTIONS

Adverse reactions based on all clinical trials with moxifloxacin 400 mg sorted by frequencies are listed below:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

- Common
- Uncommon
- Rare
- Very rare

System Organ Class	Common	Uncommon	Rare	Very Rare
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis			
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged/INR increased		Prothrombin level increased/INR decreased Agranulocytosis
Immune system disorders		Allergic reaction	Anaphylaxis incl. very rarely life-threatening shock Allergic oedema / angiooedema (incl. laryngeal oedema, potentially life-threatening)	
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia
Psychiatric disorders*		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts), Hallucination	Depersonalization Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts)

Nervous system disorders*	Headache Dizziness	Par- and Dysaesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and labyrinth disorders*			Tinnitus Hearing impairment incl. deafness (usually reversible)	
Cardiac disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes, Cardiac arrest
Vascular disorders		Vasodilatation	Hypertension Hypotension	Vasculitis
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)		
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-	

			threatening complications)	
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendonitis Muscle cramp Muscle twitching Muscle weakness	Tendon rupture , Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis
Renal and urinary disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure	
General disorders and administration site conditions*		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating	Oedema	

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

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions.

Post Marketing Experience: Exacerbation of myasthenia gravis

WARNINGS & PRECAUTIONS

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

The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section.

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was $6 \text{ msec} \pm 26 \text{ msec}$, 1.4% compared to baseline. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin. Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

If signs of cardiac arrhythmia occur during treatment with moxifloxacin, treatment should be stopped and an ECG should be performed.

Hypersensitivity/allergic reactions

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

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin. Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Patients predisposed to seizures

Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts. In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Antibiotic-associated diarrhoea incl. colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Exacerbation of myasthenia gravis:

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

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

Patients with renal impairment

Elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Dysglycemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with moxifloxacin. In moxifloxacin-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitivity reactions

Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.

Patients with pelvic inflammatory disease

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

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a 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 special cSSSi

Clinical efficacy of intravenous moxifloxacin in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Interference with biological tests

Moxifloxacin therapy may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving moxifloxacin.

Patients with MRSA infections

Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started.

Paediatric population

Due to adverse effects on the cartilage in juvenile animals the use of moxifloxacin in children and adolescents < 18 years is contraindicated.

Aortic aneurysm and dissection

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

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

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors.

Moxifloxacin should be discontinued immediately at the first sign or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Peripheral neuropathy

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

PREGNANCY

The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals and reversible joint injuries described in children receiving some

fluoroquinolones, moxifloxacin must not be used in pregnant women.

Nursing Mothers

There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breast-feeding is contraindicated during moxifloxacin therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision) or acute and short lasting loss of consciousness (syncope). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

OVERDOSE AND TREATMENT

No specific countermeasures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400 mg oral moxifloxacin will reduce systemic availability of the drug by more than 80%. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

STORAGE

Store below 30°C in a dry place, Protect from light. KEEP OUT OF REACH OF CHILDREN.

PRESENTATION

Alu/ Alu blister pack of 5 Tablets. Such 2 blisters are packed in a carton along with a pack insert.

Alu/ Alu blister pack of 5 Tablets. Such 1 blister are packed in a carton along with a pack insert.

For further information please consult your physician or pharmacist.

MANUFACTURED BY



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PRODUCT REGISTRATION HOLDER

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