

Primoxizar 400 mg

Film Coated Tablet

Qualitative and quantitative composition

Each film-coated tablet contains moxifloxacin HCl (437.9 mg) eq.to Moxifloxacin 400 mg.

Pharmaceutical form

Yellow oblong film coated tablets

Clinical particulars

Therapeutic indications (anti biotic)

Primoxizar tablets are indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin (see Special warnings and precautions for use, Undesirable effects and Pharmacodynamic properties). Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections or when these have failed:

- **Acute bacterial sinusitis (adequately diagnosed)**

In acute bacterial sinusitis Primoxizar should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

- **Acute exacerbations of chronic obstructive pulmonary disease including bronchitis (adequately diagnosed)**

In acute exacerbation of chronic obstructive pulmonary disease including bronchitis Primoxizar should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

- **Community acquired pneumonia, except severe cases**

- **Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.**

Primoxizar is not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of *Neisseria gonorrhoeae* unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded (see Special warnings and precautions for use and Pharmacodynamic properties).

Primoxizar Film Coated Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:

- **Community-acquired pneumonia**
- **Complicated skin and skin structure infections**

Primoxizar should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

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

Posology and method of administration

Posology (adults)

The recommended dose is one 400 mg film-coated tablet once daily.

Renal/hepatic impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. (See Pharmacokinetic properties for more details).

There is insufficient data in patients with impaired liver function (see Contraindications).

Other special populations

No adjustment of dosage is required in the elderly and in patients with low bodyweight.

Paediatric population

Moxifloxacin is contraindicated in children and adolescents (< 18 years). Efficacy and safety of moxifloxacin in children and adolescents have not been established (see Contraindications).

Method of administration

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

Duration of administration

Primoxizar should be used for the following treatment durations:

- | | |
|--|-------------|
| - Acute exacerbation of chronic bronchitis | 5 - 10 days |
| - Community acquired pneumonia | 10 days |
| - Acute bacterial sinusitis | 7 days |
| - Mild to moderate pelvic inflammatory disease | 14 days |

Sequential (intravenous followed by oral) therapy

The recommended total duration of intravenous and oral treatment is 7-14 days for community-acquired pneumonia and 7-21 days for complicated skin and skin structure infections

The recommended dose (400 mg once daily) and duration of therapy for the indication being treated should not be exceeded.

Contraindications

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients listed in list of excipients.
- Pregnancy and lactation (see Fertility, 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 medicinal products that prolong the QT interval (see also 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 C) and in patients with transaminases increase > 5 fold ULN.

Special warnings and precautions for use

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.

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

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.

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 (see also 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 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 (see also Contraindications). The magnitude of QT prolongation may increase with increasing concentrations of the medicinal product. 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 cases of clinical manifestation of severe hypersensitivity reactions 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 (see Undesirable effects). 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.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN; also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and Acute Generalised Exanthemous Pustulosis (AGEP), which could be life-threatening or fatal, have been reported with moxifloxacin (see Undesirable effects). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, Moxifloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or AGEP with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

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 paraesthesia, hypaesthesia, dysaesthesias, or weakness have been reported in patients receiving quinolones and fluoroquinolones. 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 in order to prevent the development of an irreversible condition (see Undesirable effects).

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 (see Undesirable effects). 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.

Medicinal products inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and in 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 (see Effects on ability to drive and use machines and Undesirable effects).

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 Primoxizar 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.

Aortic aneurysm and dissection, and heart valve regurgitation/ incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/ incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see Undesirable effects).

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 congenital heart disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

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

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

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

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

Prolonged, disabling and potentially irreversible serious adverse drug reactions

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

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 (see Pharmacodynamic properties).

Paediatric population

The use of moxifloxacin in children and adolescents < 18 years is contraindicated (see Contraindications).

Interaction with other medicinal products and other forms of interaction

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 (see also Contraindications):

- 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.

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.

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 medicinal products is not recommended (except for overdose cases, see also Overdose).

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

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.

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.

Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole.

Interaction with food

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

Fertility, pregnancy and lactation

Pregnancy

The safety of moxifloxacin in human pregnancy has not been evaluated. The potential risk for humans is unknown. Due to the reversible joint injuries described in children receiving some fluoroquinolones, moxifloxacin must not be used in pregnant women (see Contraindications).

Breastfeeding

There is no data available in lactating or nursing women. In the absence of human data breastfeeding is contraindicated during moxifloxacin therapy (see Contraindications).

Fertility

Animal studies do not indicate impairment of fertility.

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, see Undesirable effects). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

Undesirable effects

Adverse reactions observed in clinical trials and derived from post-marketing reports with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:

Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

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

- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
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 Pancytopenia	
Immune System Disorders		Allergic reaction (see Special warnings and precautions for use)	Anaphylaxis incl. very rarely life-threatening shock (see Special		

			warnings and precautions for use) Allergic oedema / angiooedema (incl. laryngeal oedema, potentially life-threatening, see Special warnings and precautions for use)		
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia Hypoglycaemic coma	
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, see Special warnings and precautions for use) Hallucination Delirium	Depersonalization Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see Special warnings and precautions for use)	
Nervous System Disorders*	Headache Dizziness	Par- and Dyaesthesia 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 (see Special warnings and precautions for use) Disturbed attention Speech disorders Amnesia	Hyperaesthesia	

			Peripheral neuropathy and polyneuropathy		
Eye Disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see Special warnings and precautions for use)	Photophobia	Transient loss of vision (especially in the course of CNS reactions, see Special warnings and precautions for use and Effects on ability to drive and use machines) Uveitis and bilateral acute iris transillumination (see Special warnings and precautions for use)	
Ear and Labyrinth Disorders*			Tinnitus Hearing impairment incl. deafness (usually reversible)		
Cardiac Disorders**	QT prolongation in patients with hypokalaemia (see Contraindications and Special warnings and precautions for use)	QT prolongation (see Special warnings and precautions for use) Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes (see Special warnings and precautions for use) Cardiac arrest (see Special warnings and precautions for use)	
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. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see Special warnings and		

			precautions for use)		
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, see Special warnings and precautions for use)	
Skin and Subcutaneous Tissue Disorders		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see Special warnings and precautions for use)	Acute Generalised Exanthemous Pustulosis (AGEP)
Musculoskeletal and connective Tissue Disorders*		Arthralgia Myalgia	Tendonitis (see Special warnings and precautions for use) Muscle cramp Muscle twitching Muscle weakness	Tendon rupture (see Special warnings and precautions for use) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see Special warnings and precautions for use)	Rhabdomyolysis
Renal and Urinary Disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure (see Special warnings and precautions for use)		
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 tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Special warnings and precautions for use).

**Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/ incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see Special warnings and precautions for use).

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: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia, photosensitivity reactions (see Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to: **Pharma Cure Pharmaceutical Industries**

Tel.: 002-048-2657089 / 002-01145004525 / 002-013-3236852 / 002-013-3223754

Fax: 002-013-3236711 / 002-048-2657088

E.mail: info@pharmacureonline.com

pharmacovigilance@pharmacureonline.com

pv.center@eda.mohip.gov.eg

Overdose

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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones,

Mechanism of action

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
<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>
<p>*Activity has been satisfactorily demonstrated in susceptible strains in clinical studies in the approved clinical indications.</p> <p># ESBL-producing strains are commonly resistant to fluoroquinolones</p> <p>+ Resistance rate > 50% in one or more countries</p>

Pharmacokinetic properties

Absorption and Bioavailability

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

Distribution

Moxifloxacin is distributed to extravascular spaces rapidly.

Biotransformation

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.

There is no indication of oxidative metabolism.

Elimination

Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 hours. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys.

Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

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

There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

Pharmaceutical particulars

List of excipients

- Lactose monohydrate
- Avicel Ph102, polyvinyl pyrrolidone (povidone K30)
- Explotab
- Colloidal silicon dioxide
- Magnesium stearate
- Purified talc
- α hydroxy propyl methyl cellulose E5
- Titanium dioxide, polyethylene glycol 6000
- Quinoline yellow

Incompatibilities

Not applicable.

Shelf life

2 years

Special precautions for storage

Store at temperature not exceeding 30° C in dry place

Nature and contents of container

Carton box containing 1,2 (Al/transparent PVC) strips each one of 5 film coated tablets and an insert leaflet

Special precautions for disposal and other handling

No special requirements.

**Manufactured by: Pharma Cure
Pharmaceutical Industries**