MOXIFLOXACIN

INDICATIONS:

Moxifloxacin 400 mg film-coated 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 sections 4.4, 4.8 and 5.1). 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)

- Acute exacerbations of chronic bronchitis (adequately diagnosed)

- 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.

Moxifloxacin 400 mg film-coated tablets are 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 sections 4.4 and 5.1).

Moxifloxacin 400 mg 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

Moxifloxacin 400 mg film-coated tablets 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.

SAFETY ALERT:

1. **Adverse Drug Reactions**:

- 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 (≥ 1/100 to < 1/10)
- - Uncommon (≥ 1/1,000 to < 1/100)
- - Rare (≥ 1/10,000 to < 1/1,000)

- - Very rare (< 1/10,000)

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 (see section 4.4)	Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema / angiooedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)	
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	
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 section 4.4) Hallucination	Depersonalization Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4)

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 (see section 4.4) 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, see section 4.4)		Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment incl. deafness (usually reversible)	
Cardiac Disorders	QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes (see section 4.4) Cardiac arrest (see section 4.4)
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 section 4.4)	

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 section 4.4)
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 section 4.4)
Musculoskeletal and connective Tissue Disorders		Arthralgia Myalgia	Tendonitis (see section 4.4) Muscle cramp Muscle twitching Muscle weakness	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)
Renal and Urinary Disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure (see section 4.4)	
General Disorders and Administration Site Conditions		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating	Oedema	

- 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, (see section 4.4).
- Reporting of suspected adverse reactions
- Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard
- **4.9 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 medicinal product 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.

2. **Drug interactions**:

- 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 section 4.3):
- - 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 section 4.9).
- 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.
- In studies conducted in diabetic volunteers, 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.
- *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.
- *In vitro* studies with human cytochrome P450 enzymes support these findings. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.
- Interaction with food
- Moxifloxacin has no clinically relevant interaction with food including dairy products

3. Contraindications:

- - Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients listed in section 6.1.
- - Pregnancy and lactation (see section 4.6).
- - 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 section 4.5).
- Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5fold ULN.

4. Precautions:

- 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 msec ± 26 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 (see also sections 4.3 and 4.5).
- 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 section 4.3). 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 section 4.8). 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 (see section 4.8). 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 in order to prevent the development of an irreversible condition (see section 4.8).
- 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 section 4.8). 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.
- Tendon inflammation, tendon rupture
- Tendon inflammation and rupture (especially Achilles tendon), sometimes bilateral, may occur with quinolone therapy including moxifloxacin, even within 48 hours of starting treatment and have been reported up to several months after discontinuation of therapy. The risk of tendinitis and tendon rupture is increased in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin, rest the affected limb(s) and consult their doctor immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon (see sections 4.3 and 4.8).
- 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 sections 4.7 and 4.8).
- 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] 400 mg film-coated 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 (see section 5.1).
- Paediatric population
- Due to adverse effects on the cartilage in juvenile animals (see section 5.3) the use of moxifloxacin in children and adolescents < 18 years is contraindicated