SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Moxifloxacin 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg of moxifloxacin.

Excipients with known effect:Each film-coated tablet contains 77.16 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink colored, capsule shaped, biconvex, beveled edge, film-coated tablet marked with 'MF' on one side and plain on other side with dimensions 17 mm (L) and 8 mm (W) approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

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

Moxifloxacin is 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).

- 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 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 sections 4.4 and 5.1).

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

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

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

4.2 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 section 5.2 for more details).

There is insufficient data in patients with impaired liver function (see section 4.3).

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 section 4.3).

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

Duration of administration
Moxifloxacin should be used for the following treatment durations:

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

Moxifloxacin have been studied in clinical trials for up to 14 days of treatment.

Sequential (intravenous followed by oral) therapy

In clinical studies with sequential therapy most patients switched from intravenous to oral therapy within 4 days (community-acquired pneumonia) or 6 days (complicated skin and skin structure infections). 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 per day) and duration of therapy for the indication being treated should not be exceeded.

4.3 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 drugs 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 patients with transaminases increase > 5fold ULN.

4.4 Special warnings and precautions for use

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 section 4.8). 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 section 4.3).

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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Moxifloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

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 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 (including torsade de pointes) and cardiac arrest (see also section 4.3). 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.

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 section 4.8).

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 valve 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.

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 manifestations 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.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS), Acute Generalised Exanthematous Pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which could be life-threatening or fatal, have been reported with moxifloxacin (see section 4.8). 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, AGEP or DRESS 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, hypoaesthesia, dysaesthesia, 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 potentially 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 including 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.

Patients with myasthenia gravis
Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptomscan be exacerbated.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to the 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 (see sections 4.3 and 4.8). The risk of tendinitis and tendon rupture is increased in older patients, patients 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 (see sections 4.7 and 4.8).

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with moxifloxacin (see section 4.8), In moxifloxacin treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. 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 (see section 4.8).

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 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 a special cSSSI
Clinical efficacy of intravenous moxifloxacin in the treatment of severe burn wound infections, fasciitis, and diabetic foot infection 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 (see section 4.3).

Information about excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 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 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 ledto 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, see also section 4.9).

After repeated dosing in healthy volunteers, moxifloxacin increased Cmax 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity (see section 5.3). 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 (see section 4.3).

Breastfeeding

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 (see section 4.3).

Fertility

Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 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 reasul 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 section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects

Adverse reactions based on all 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)
- Not known: frequency cannot be estimated from the available data

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Very Rare**	**N**ot 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 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)		
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
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 section 4.4) Hallucination Delirium	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	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions	Hyperaesthesia	

		Vertigo Somnolence	(see section 4.4) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy		
Eye Disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)	Photophobia	Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7) Uveitis and bilateral acute iris transillumination (see section 4.4)	
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	Decreased appetite and food intake Constipation	Dysphagia Stomatitis		

	Gastrointestinal and abdominal pains Diarrhoea	Dyspepsia Flatulence Gastritis Increased amylase	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)	Acute Generalised Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption, Photosensitivity reactions (see section 4.4)
Musculoskeletal, Connective Tissue and Bone Disorders*		Arthralgia Myalgia	Tendonitis, Tendon rupture (see section 4.4) Muscle cramp Muscle twitching Muscle weakness	Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)	Rhabdomyolysis
Renal and		Dehydration	Renal impairment		

Urinary Disorders			(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: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia.

*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, fatigue, psychaitric symptoms, memory impairment, 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 Section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category).

** 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 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 the Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01 MA14

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 *nor*A or *pmr*A 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.

Breakpoints

EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (v. 9.0, 01 January 2019):

Organism	**Susceptible**	**Resistant**
S. aureus	≤ 0.25 mg/l ≥ 25 mm	> 0.25 mg/l < 25 mm
Coagulase-negative *staphylococci*	≤ 0.25 mg/l ≥ 28 mm	> 0.25 mg/l < 28 mm
S. pneumoniae	≤ 0.5 mg/l ≥ 22 mm	> 0.5 mg/l < 22 mm
Streptococcus group A, B, C, G	≤ 0.5 mg/l ≥ 19 mm	> 0.5 mg/l < 19 mm
H. influenzae	≤ 0.125 mg/l ≥ 28 mm	> 0.125 mg/l < 28 mm
M. catarrhalis	≤ 0.25 mg/l ≥ 26 mm	> 0.25 mg/l < 26 mm
Enterobacteriaceae(new taxonomy: Enterobacterales)*	≤ 0.25 mg/l ≥ 22 mm	> 0.25 mg/l < 22 mm
Non-species related breakpoints**	≤ 0.25 mg/l	> 0.25 mg/l
Corynebacterium spp.	≤ 0.5 ≥ 25 mm	> 0.5 < 25 mm

* Recent taxonomic studies have narrowed the definition of the family Enterobacteriaceae. Some previous members of this family are now included in other families within the Order Enterobacterales. Breakpoints in this table apply to all members of the Enterobacterales.

** These breakpoints are used only when there are no species-specific breakpoints or other recommendations (a dash or a note) in the species-specific tables.

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
Aerobic Gram-positive micro-organisms *Gardnella vaginalis* *Staphylococcus aureus** (*methicillin-susceptible)* *Streptococcus agalactiae* (Group B) [*]*Streptococcus milleri* group (*S. anginosus, S. constellatus and S. intermedius*) *Streptococcus pneumoniae** *Streptococcus pyogenes** (*Group A*) *Streptococcus viridans group (S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus)*
Aerobic Gram-negative micro-organisms *Acinetobacter baumanii* *Haemophilus influenzae** *Haemophilus parainfluenzae ** *Legionella pneumophila* *Moraxella (Branhamella) catarrhalis**
Anaerobic micro-organisms *Fusobacterium* spp. *Prevotella* spp.
"Other" micro-organisms *Chlamydophila (Chlamydia) pneumoniae** *Chlamydia trachomatis** *Coxiella burnetii* *Mycoplasma genitalium* *Mycoplasma hominis* *Mycoplasma pneumoniae*[*]
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis** *Enterococcus faecium** *Staphylococcus aureus* (methicillin-resistent)[+]
Aerobic Gram-negative microorganisms *Enterobacter cloacae** *Escherichia coli** *Klebsiella pneumoniae**[#] *Klebsiella oxytoca* *Neisseria gonorrhoeae**[+] *Proteus mirabilis**
Anaerobic micro-organisms Bacteroides fragilis* Peptostreptococcus spp.*

Inherently resistant organisms
Aerobic Gram-negative microorganisms *Pseudomonas aeruginosa*
[*]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

5.2 Pharmacokinetic properties

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

Pharmacokinetics are 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 (Vss) 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 dose of 400 mg Moxifloxacin:

Tissue	**Concentration**	**Site: plasma ratios**
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75 to 1.3
Blister fluid	1.6[1] mg/l	1.7[1]
Bronchial mucosa	5.4 mg/kg	1.7 to 2.1
Alveolar macrophages	56.7 mg/kg	18.6 to 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 dose of 400 mg
[1] 10 hours after administration

[2] unbound concentration
[3] from 3 h up to 36 h post dose
[4] at the end of the infusion

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.

In clinical Phase I and *in vitro* studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism.

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%.

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 m^2). 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 m^2).

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.

5.3 Preclinical safety data

Effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys, CNS toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin or after prolonged treatment.

Moxifloxacin, like other quinolones, was genotoxic in *in vitro* tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and - at higher concentrations - by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

Many quinolones are photoreactive and can induce phototoxic, photomutagenic and photocarcinogenic effects. In contrast, moxifloxacin was proven to be devoid of phototoxic and photogenotoxic properties when tested in a comprehensive programme of *in vitro* and *in vivo* studies. Under the same conditions other quinolones induced effects.

At high concentrations, moxifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT interval. Toxicological studies performed in dogs using oral doses of 90 mg/kg leading to plasma concentrations ≥16 mg/l caused QT prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50-fold the human dose (> 300 mg/kg), leading to plasma concentrations of ≥ 200 mg/l (more than 40-fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times the maximum recommended therapeutic dose of 400 mg (assuming a 50 kg bodyweight) on a mg/kg basis, with plasma concentrations two to three times higher than those at the maximum therapeutic dose.

Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. In dogs, high oral doses (≥60 mg/kg) leading to plasma concentrations ≥20 mg/l caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the

incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Lactose monohydrate

Croscarmellose sodium

Microcrystalline cellulose (Avicel PH 101)

Magnesium sterate

Film coating:

HPMC 2910/Hypromellose(E464)

Titanium dioxide (E171)

Macrogol/PEG 4000 (E1521)

Iron oxide Red (E172)

Iron oxide Yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cartons containing PVC/PE/PVDC-Aluminum foil blisters.

Moxifloxacin is available in packs containing 5, 6, 7, and 10 film-coated tablets.

Moxifloxacin is also available in hospital packs containing 25, 50, 70, 80 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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