1.8 Summary of Product Characteristic

Name of the Medicinal Product
Moxifloxacin Tablets 400 mg (Zeebact)

Qualitative and Quantitative Composition
Each film coated tablet contains:
Moxifloxacin Hydrochloride USP
equivalent to Moxifloxacin 400 mg

Batch Formula:

Sr. No.	Ingredients	Specifications	Standard Quantity (mg/Tablet)
DRY MIXING			
01	Moxifloxacin Hydrochloride USP equivalent to Moxifloxacin	USP	455.00 mg = 400.00 mg
02	Croscarmellose Sodium	BP	30.000 mg
03	Maize Starch	BP	50.000 mg
04	Microcrystalline Cellulose	BP	50.000 mg
05	Crospovidone	USP	5.000 mg
06	Pregelatinised Starch	BP	5.000 mg
BINDER PREPRATION			
07	Purified Water	In House	Q.S.
LUBRICATION			
08	Purified Talc	BP	7.000 mg
09	Magnesium Stearate	BP	10.000 mg
10	Colloidal Anhydrous Silica	BP	3.000 mg
11	Croscarmellose Sodium	BP	30.000 mg
Theoretical Standard Average Weight (Core)			**645.000**
COATING			
12	Unique Coat FCNAQ White	In House	15.000
13	Isopropyl Alcohol	BP	0.05 ml
14	Dichloromethane	BP	0.05 ml
15	Colour–Lake Quinoline Yellow	In House	0.10 mg
Theoretical Standard Average Weight (Coated)			**660.000**

Pharmaceutical Form
Oral Tablet

Description
Yellow coloured, oval, caplet shape film coated scored tablets.

Drug formulation: Oral Tablets

Pharmacotherapeutic group:

Pharmacotherapeutic Group: Quinolone antibacterials, fluoroquinolones

ATC Code: J01MA14

CLINICAL PARTICULARS

Therapeutic indications

Zeebact 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.

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.
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis.
- In acute exacerbations of obstructive pulmonary disease including bronchitis, Moxifloxacin 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.

Moxifloxacin 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*.

Moxifloxacin 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 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.

Posology and method of administration

Posology

The recommended dose is one Zeebact 400mg 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.

There is insufficient data in patients with impaired liver function.

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.

Method of administration

The tablets should be swallowed whole with a glass of water and may be taken independent of meals. DO NOT chew or crush the tablets.

Duration of administration

Zeebact film-coated tablets 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

Zeebact film-coated tablets have been studied in clinical trials for up to 14 days treatment.

Contra-indications

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

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

- Congenital or documented acquired QT prolongation

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

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

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

Special warnings and special 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. Treatment of these patients with Moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

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

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.

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.

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.

Moxifloxacin should be used with caution in patients with ongoing pro-arrhythmic conditions (especially women and elderly patients), such as acute myocardial is chaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade depointes) and cardiac arrest. The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

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

Hypersensitivity/allergic reactions

Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration.

In these cases 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. 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 Exanthematous Pustulosis (AGEP), which could be life-threatening or fatal, have been reported

with moxifloxacin. 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.

Patients predisposed to seizures

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Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Moxifloxacin should be advised to inform their doctor 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.

Psychiatric reactions

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

Antibiotic-associated diarrhoea incl. colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of broad-spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of Moxifloxacin.

If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including Moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

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 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.

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.

Patients with renal impairment

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

Vision disorders

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

Dysglycemia

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

Prevention of photosensitivity reactions

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

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.

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 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.

Paediatric population

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

Important information about some of the ingredients of Ibuprofen tablets

Sodium:

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Interactions 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 led to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases, 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 supported 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.

Pregnancy and lactation

Pregnancy

The safety of Moxifloxacin in human pregnancy has not been evaluated.

Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight bearing cartilage of immature animals and reversible joint injuries described in children receiving some fluoroquinolones, Moxifloxacin must not be used in pregnant women.

Breast-feeding

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 fluoroquinolone to the weight-bearing cartilage of immature animals, breast-feeding I contraindicated during Moxifloxacin therapy.

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. Patients should be advised to see how they react to Moxifloxacin before driving or operating machinery.

Undesirable effects

Summary of the safety profile

Adverse reactions based on all clinical trials and derived from post-marketing reports with Moxifloxacin (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:

- Very common (≥1/10),
- 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 (cannot be estimated from the available data).

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal andidiasis				
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	Anaphylaxis incl. very rarely life-threatening shock Allergic oedema / angioedema (incl. laryngeal oedema, potentially life-threatening		

Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricemia	Hypoglycemia Hypoglycaemiccoma	
Psychiatric disorders*		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotionall ability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, Hallucination Delirium	Depersonalization Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
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	Hyperaesthesia	

			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		Transient loss of vision (especially in the course of CNS reactions	
Ear and labyrinth disorders *			Tinnitus Hearing impairment incl. deafness (usually reversible)		
Cardiac disorders **	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e. acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de Pointes Cardiac arrest	
Vascular disorders **		Vasodilatation	Hypertension Hypotension	Vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea (including asthmatic conditions)			

Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gammaglutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry Skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal ecrolysis (potentially life-threatening	Acute Generalised Exanthematous Pustulosis (AGEP)
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendonitis Muscle cramp Muscle twitching Muscle weakness	Tendon rupture Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis	Rhabdomyolysis

Renal and urinary disorders		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure		
General disorders and administration site conditions*		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating	Oedema		

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as 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.

** 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.

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.

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, ATC code: J01MA14

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 (01.01.2011):

Organism	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0.5 mg/l ≥ 24 mm	> 1 mg/l < 21 mm
S. pneumoniae	≤ 0.5 mg/l ≥ 22 mm	> 0.5 mg/l ≥ 22 mm
Streptococcus Groups A, B, C, G	≤ 0.5 mg/l ≥ 18 mm	> 1 mg/l < 15 mm
H. influenzae	≤ 0.5 mg/l ≥ 25 mm	≤ 0.5 mg/l ≥ 25 mm
M. catarrhalis	≤ 0.5 mg/l ≥ 23 mm	> 0.5 mg/l < 23 mm
Enterobacteriaceae	≤ 0.5 mg/l ≥ 20 mm	> 1 mg/l < 17 mm
Non-species related breakpoints*	≤ 0.5 mg/l	> 1 mg/l
* Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined.		

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species 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

Gardnerella vaginalis

*Staphylococcus aureus** (methicillin-susceptible)

Streptococcus agalactiae (Group B)

Streptococcus milleri group* (*S. anginosus, S. constellatus and S. intermedius*)

*Streptococcus pneumoniae**

*Streptococcus pyogenes** (Group A)

Streptococcus viridans group *(S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus)*

Aerobic Gram-negative 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-resistant)+

Aerobic Gram-negative micro-organisms

*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 micro-organisms

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

Pharmacokinetics 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 oral dose of 400 mg moxifloxacin:

Tissue	**Concentration**	**Site: Plasma ratio**
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75 - 1.3
Blister fluid	1.61 mg/l	1.71
Bronchial mucosa	5.4 mg/kg	1.7 -2.1
Alveolar macrophages	56.7 mg/kg	18.6 - 70.0
Epithelial lining fluid	20.7 mg/l	5 - 7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal polyps	9.1 mg/kg	2.6
Interstitial fluid	1.02 mg/l	0.8 -1.4[2,3]
Female genital tract*	10.24 mg/kg	1.72[4]
*** intravenous administration of a single 400 mg dose** **1 10 h after administration** **2 unbound concentration** **3 from 3 h up to 36 h post dose** **4 at the end of infusion**		

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.

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 initiationpromotion 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.

Incompatibilities

Not applicable

Shelf life

3 years.

Storage conditions

Store at a temperature not exceeding 30°C in a cool & dry place, Protect from light.

Special precautions for storage

This medicinal product does not require any special storage conditions.

Special precautions for disposal and other handling

Not applicable.

Packing

1 Alu-Alu Blister strips of 5 tablets per carton.

Marketing authorisation holder

Kenya

Name and address of manufacturer

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