MOXIFCIN
FILM COATED TABLET 400MG

Active Ingredient:
Each film coated tablet contains:
Moxifloxacin Hydrochloride……..... 436.8mg
(eq. to Moxifloxacin 400mg)

List of excipients:
Lactose, Polyvinylpyrrolidone, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate & Purified Water.
Film Coating (Polyvinyl Alcohol, Talc, Titanium Dioxide, Macrogol, Lecithin, Iron Oxide Red, Iron Oxide Yellow & Black Iron Oxide)

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14

Pharmacodynamics:
Mechanism of action
Moxifloxacin is active against a wide range of Gram-positive and Gram-negative pathogens.
The bactericidal action of moxifloxacin results from the inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription and repair. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the norA or pmrA genes seen in certain Gram-positive bacteria.
Moxifloxacin exhibits a concentration dependent killing rate.

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.
Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.
Moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.

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

Effect on the intestinal flora in humans
In two volunteer studies, the following changes in the intestinal flora were seen following oral dosing with moxifloxacin. *E. coli*, *Bacillus spp.*, *Bacteroides vulgatus*, *Enterococci*, and *Klebsiella spp*. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium*, and *Peptostreptococcus*. These changes returned to normal within two weeks. Clostridium difficile toxin was not found. Moxifloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the "Indications" section.

In-vitro Susceptibility Data:

Susceptible	Intermediate	Resistant
Gram-positive bacteria		
Gardnerella vaginalis	*Enterococcus faecalis** (Vancomycin, Gentamycin, susceptible strains only)	*Staphylococcus aureus* (methicillin/ofloxacin resistant strains)+
*Streptococcus pneumoniae** including multi-drug resistant streptococcus pneumoniae strains [MDRSP] including strains known as PRSP (Penicillin-resistant S. pneumoniae), and strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/ sulfamethoxazole	*Enterococcus avium**	Coagulase negative Staphylococci (*S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans*) methicillin resistant strains
Streptococcus pyogenes (group A)*	*Enterococcus faecium**	
Streptococcus milleri group (S. anginosus, S. constellatus*, and S. intermedius*)*		
Streptococcus viridans group (S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus, S. constellatus)		
Streptococcus agalactiae		
Streptococcus dysgalactiae		
*Staphylococcus aureus (methicillin susceptible strains) **		
Coagulase negative Staphylococci *(S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans)* methicillin susceptible strains.		
Gram-negative bacteria		
Haemophilus influenzae (including ß lactamase negative and positive strains)*	*Escherichia coli **	*Pseudomonas aeruginosa*
*Haemophilus parainfluenzae**	*Klebsiella pneumoniae**	
Moraxella catarrhalis (including ß lactamase negative and positive strains)*	*Klebsiella oxytoca*	
Bordetella pertussis	*Citrobacter freundii**	
Legionella pneumophila	*Enterobacter species (E. aerogenes, E. intermedius, E. sakazaki)*	
Acinetobacter baumanii	*Enterobacter cloacae**	
Proteus vulgaris	*Pantoea agglomerans*	
	Pseudomonas fluorescens	
	Burkholderia cepacia	
	Stenotrophomonas maltophilia	
	*Proteus mirabilis**	
	Morganella morganii	
	*Neisseria gonorrhoea***	
	Providencia species (P. rettgeri, P. stuartii)	
Anaerobes		
Fusobacterium spp	*Bacteroides sp (B. fragilis*, B. distasoni*, B. thetaiotaomicron*, B. ovatus*, B. uniformis*, B. vulgaris*)*	

Porphyromonas spp	*Peptostreptococcus spp.**	
Prevotella spp	*Clostridium sp**	
Propionibacterium spp.		
Atypicals		
*Chlamydia pneumoniae**		
*Chlamydia trachomatis***		
*Mycoplasma pneumoniae**		
Mycoplasma hominis		
Mycoplasma genitalum		
Coxiella burnettii		

*/** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
+ Moxifloxacin is not recommended for the treatment of methicillin resistant *S. aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections. The above information is provided as a guide on the probability of an organism being susceptible to moxifloxacin. Comparison of PK/PD surrogates for intravenous and oral administration of a 400 mg Moxifloxacin single dose. In patients requiring hospitalisation AUC / MIC_{90} parameters greater than 125 and Cmax / MIC_{90} of 8 - 10 is predictive for clinical cure (Schentag). In outpatients these surrogate parameters are generally smaller, i.e. AUC / MIC_{90} greater than 30 - 40 (Dudley and Ambrose).
The following table provides the respective PK/PD surrogates for intravenous and oral administration of 400 mg moxifloxacin calculated from single dose data:

Mode of administration	**Intravenous**		**Oral**	
Parameter (median)	AUIC[h]	Cmax / MIC_{90}[a)]	AUIC[h]	Cmax / MIC_{90}
MIC_{90} 0.125mg/L	313	32.5	279	23.6
MIC_{90} 0.25mg/L	156	16.2	140	11.8
MIC_{90} 0.5mg/L	78	8.1	70	5.9

a) 1h infusion

Pharmacokinetics:
Absorption and bioavailability
Following oral administration Moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approx. 91%.
Pharmacokinetics are linear in the range of 50 - 1200 mg single dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 hours postapplication. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively.
Concomitant administration of Moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of fluoroquinolones, this effect is clinically not relevant. Therefore, Moxifloxacin can be administered independently from meals.

Distribution
Moxifloxacin is distributed very rapidly to extravascular spaces. Exposure to drug in terms of AUC (AUCnorm = 6 kg*h/l) is high with a volume of distribution at steady state (Vss) of approximately 2 L/kg. In saliva peak concentrations higher than those of plasma may be reached. In in vitro and ex-vivo experiments over a range of 0.02 to 2 mg/l a protein binding of approximately 45 % independent from the concentration of the drug was determined. Moxifloxacin is mainly bound to serum albumin. Due to this low value high free peak concentrations > 10 x MIC are observed.
Moxifloxacin reaches high concentrations in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide blister fluid) where total concentrations exceeding those of the plasma concentrations are reached. High free drug concentrations are measured in interstitial body water (saliva, intramuscular, subcutaneous). In addition, high drug concentrations were detected in abdominal tissues and fluids and female genital tract.

Tissue	**Concentration (p.o.)**		**Site: Plasma ratio (p.o.)**
Plasma	3.1	mg/L	--
Saliva	3.6	mg/L	0.75 - 1.3
Blister fluid	1.6[1]	mg/L	1.7[1]
Bronchial mucosa	5.4	mg/kg	1.7 - 2.1
Alveolar Macrophages	56.7	mg/kg	18.6 - 70.0
Epithelial lining fluid	20.7	mg/L	5 - 7
Maxillary sinus	7.5	mg/kg	2.0
Ethmoid sinus	8.2	mg/kg	2.1
Nasal Polyps	9.1	mg/kg	2.6
Interstitial fluid	1.0[2]	mg/L	0.8 - 1.4[2,3]
Tissue	**Concentration (p.o.)**		**Site: Plasma ratio (p.o.)**
Plasma	4.1	mg/L	--
Saliva	5.0	mg/L	0.82 - 1.37
Blister fluid	1.75[1]	mg/L	1.71
Interstitial fluid	1.0[2]	mg/L	0.8 - 2.5[2,3]
Abdominal tissue[4]	7.03	mg/L	1.56
Abdominal exudate[5]	3.32	mg/L	1.45
Abscess fluid[6]	1.94	mg/L	0.74
Female genital tract[4]	10.2	mg/L	1.72
Remarks: [1]10 h after administration [2] unbound concentration [3] from 3h up to 36h post dose [4] at the end of infusion [5] 2 hours after administration [6] 3 h after administration			

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. Neither in in vitro nor in clinical Phase I studies metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving Cytochrome P-450 enzymes were observed. Independent from the route of administration the metabolites M1 and M2 are found in the plasma at concentrations lower than the parent drug. Preclinical investigations adequately covered both metabolites thus excluding potential implications with respect to safety and tolerability.

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. Concomitant administration of ranitidine and probenecid did not alter renal clearance of the drug.
Mass balance of the mother compound and Phase II metabolites of Moxifloxacin yielded an almost complete recovery of approximately 96-98% independent from the route of administration with no indication of oxidative metabolism.

A detailed overview of the mass balance according to elimination pathways (renal vs non-renal, metabolic vs. non-metabolic) and mode of application is given in the table below.

Recovery of a 400 mg single dose (arithmetric mean ± standard deviation (SD)

	Moxifloxacin	**Sulfo-compound (M1)**	**Glucuronide (M2)**	∑
Urine p.o.	19.4 ±1.2	2.5 ± 0.6	13.6 ± 2.8	35.4 ±1.8
Faeces p.o.	25.4 ± 3.1	35.5 ± 3.2	-	60.9 ± 4.3
∑ p.o. (n=6)	44.8 ± 3.3	37.9 ± 3.6	13.6 ± 2.8	96.3 ± 4.3
Urine i.v.	21.9 ± 3.6	2.5 ± 0.9	13.8 ± 2.0	38.1 ± 2.1
Faeces i.v.	25.9 ± 4.3	34.4 ± 5.6	-	60.2 ± 9.2
∑ i.v. (n=5)	47.8 ± 7.2	36.8 ± 5.9	13.8 ± 2.0	98.4 ± 10.5

Geriatric patients
Pharmacokinetics of Moxifloxacin are not affected by age.

Gender
There was a 33% difference in the pharmacokinetics (AUC, Cmax) of Moxifloxacin between male and female subjects. Drug absorption was unaffected by gender. These differences in the AUC and Cmax were attributable to the differences in body weight rather than gender. They are not considered as clinically relevant.

Ethnic differences
Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Children and adolescents
Pharmacokinetics of Moxifloxacin were not studied in paediatric patients.

Patients with renal impairment
The pharmacokinetics of Moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 ml/min/1.73m2) and in patients on chronic dialysis i. e. hemodialysis and continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment
Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see "Warnings and Precautions"). There is no experience in patients with severe hepatic impairment (Child Pugh C).

Preclinical Safety Data
In a local tolerability study performed in dogs, no signs of local intolerability were seen when Moxifloxacin was administered intravenously. After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of Moxifloxacin should be avoided.

Carcinogenicity, Mutagenicity
Moxifloxacin, like other fluoroquinolones, was genotoxic 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.

ECG
At high concentrations, Moxifloxacin is an inhibitor 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 30 fold the therapeutic level after intravenous administration), reversible, non-fatal ventricular arrhythmias were seen.

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

Reprotoxicity
Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of Moxifloxacin occurs. Studies in rats (per os and i.v.) and monkeys (per os) did not show evidence of teratogenicity or impairment of fertility following administration of Moxifloxacin. Skeletal malformations were observed in rabbits that had been treated with an intravenous dose of 20 mg/kg. This study result is consistent with the known effects of fluoroquinolones on skeletal development. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic 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.

Indication:
Moxifcin Film Coated Tablet 400mg is indicated for the treatment of the following bacterial infections caused by susceptible strains:
- Respiratory tract infection:
  - Acute Bacterial Sinusitis caused by Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis.
  - Acute Bacterial Exacerbation of Chronic Bronchitis caused by S*treptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus, or Moraxella catarrhalis.*
  - Community Acquired Pneumonia (of mild to moderate severity) caused by S*treptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Moraxella catarrhalis.*
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* or *Streptococcus pyogenes.*
- Complicated skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae or Enterobactercioacae*.
- 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.

Moxifcin Film Coated Tablet 400mg 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 (eg. a cephalosporin) due to increasing Moxifloxacin resistance of Neisseria gonorrhoeae.
Moxifcin Film Coated Tablet 400mg is indicated for the treatment of the above infections if they are caused by bacteria susceptible to Moxifloxacin.

Recommended Dose:
Dose (adults):
The recommended dose for Moxifloxacin is 400 mg once daily (1 film coated tablet) for the above mentioned indications and should not be exceeded.

For complicated skin and skin structure infections, therapy should usually be initiated with intravenous formulation. When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with intravenous moxifloxacin may be switched to Moxifloxacin Tablets when clinically indicated at the discretion of the physician.

Duration of treatment:

The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations are made:

Acute exacerbation of chronic bronchitis: 5 days
Acute sinusitis: 7 days
Uncomplicated skin and skin structure infections: 7 days
Community acquired pneumonia (mild to moderate in severity): 10 days
Community acquired pneumonia: total recommended duration for sequential administration (intravenous followed by oral therapy) is 7-14 days
Complicated skin and skin structure infections: total treatment duration for sequential therapy (intravenous followed by oral therapy) is 7-21 days
Mild to moderate pelvic inflammatory disease: 14 days

The recommended duration of treatment for the indication being treated should not be exceeded. Moxifloxacin 400 mg film-coated tablets and Moxifloxacin 400 mg solution for infusion have been studied in clinical trials for up to 21 days (in complicated skin and skin structure infections).
If a dose is missed, it should be taken anytime but not later than 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Children and adolescents: Efficacy and safety of Moxifloxacin in children and adolescents have not been established (see "Contraindications").

Geriatric patients: No adjustment of dosage is required in elderly.

Ethnic differences: No adjustment of dosage is required in ethnic groups.

Patients with hepatic impairment: No dosage adjustment is required in patients with mild or moderate impaired liver function. The use of Moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C) (see "Warnings and Precautions" in Child Pugh C patients).

Patients with renal impairment: No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m²) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

Route of Administration
For oral use. The film-coated tablet should be swallowed whole with sufficient liquid/ water and may be taken independent of meals.

Contraindication:
- 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.

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 "Interactions with Other Medicines and Other Forms of Interaction").
Moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5 fold ULN.

Warnings and Precautions:
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 Adverse Effects/ Undesirable Effects). Treatment of these patients with Moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.
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
Fluoroquinolones, including Moxifloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions. Discontinue Moxifloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including Moxifloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.
Because of the widespread and rising prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae infections, monotherapy with Moxifloxacin should be avoided in patients with pelvic inflammatory disease, the addition of an appropriate antibiotic which is regularly active against N gonorrhoeae (e.g. cephalosphorin) to empirical Moxifloxacin therapy, should be considered.

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions
Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.
As the magnitude of QT prolongation may increase with increasing concentrations of the drug, the recommended dose and infusion rate (400mg within 60 minutes) should not be exceeded. However, in patients suffering from pneumonia, no correlation between plasma concentrations of moxifloxacin and QTc prolongation was observed. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade des pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Moxifloxacin treatment in clinical studies with more than 9000 patients, however, certain predisposing conditions may increase the risk for ventricular arrhythmias.
Therefore, treatment with Moxifloxacin should be avoided due to the lack of clinical experience with the drug in these patient populations:
- in patients with known prolongation of the QT interval
- in patients with uncorrected hypokalemia
- in patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents

Moxifloxacin should be used with caution as an additive effect of Moxifloxacin on the QT interval cannot be excluded for the following conditions:
- in patients treated concomitantly with drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants
- in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia
- in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded
- in women and elderly patients who, both, may be more susceptible to QTc-prolonging drugs

Treatment with Moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings. Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels. Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia.

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. 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. Due to limited clinical data the use of Moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).

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

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

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

Peripheral Neuropathy
Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including Moxifloxacin. Symptoms may occur soon after initiation of Moxifloxacin and may be irreversible. Moxifloxacin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation.

Psychiatric adverse reactions
Fluoroquinolones, including Moxifloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving Moxifloxacin, discontinue Moxifloxacin immediately and institute appropriate measures.

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.

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.

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

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 and rupture may occur even up to several months after discontinuing quinolone therapy including moxifloxacin.

Aortic aneurysm and dissectionAortic aneurysm or 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 a 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 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, Behçet´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.

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. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue Moxifloxacin and initiate appropriate therapy immediately.

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 Moxifcin F.C. Tablet 400mg is not recommended.

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 "Pharmacodynamic").

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

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

Interactions with Other Medicines and Other Forms of Interaction:
For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.
Antacids, minerals and multi-vitamins
Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to formation of chelate complexes with the multi-valent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral drugs and other preparations containing magnesium or aluminium, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin dose.
Warfarin
No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.
Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed and, if necessary, the oral anticoagulant dosage should be adjusted as appropriate.
Digoxin
The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin and vice versa. After repeated dosing in healthy volunteers moxifloxacin increased Cmax of digoxin by approximately 30 % at steady state without affecting AUC or trough levels.
Charcoal
Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80 % by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.
Food and dairy products
Absorption of moxifloxacin was not altered by food intake (including dairy products). Therefore, moxifloxacin can be taken independent from food intake.

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

- anti-arrhythmics class IA (eg. Quinidine, hydroquinone, 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 (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil)

Use during Pregnancy / Lactation:
Pregnancy
The safe use of moxifloxacin in human pregnancy has not been established. Reversible joint injuries are described in children receiving some fluoroquinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Consequently, the use of moxifloxacin during pregnancy is contraindicated.

Lactation
As with other fluoroquinolones, moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of moxifloxacin in nursing mothers is contra-indicated.

Adverse Effects/ Undesirable Effects:
Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg sorted by CIOMS III categories of frequency are listed below. ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhea. 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 (MedDRA)	Common	Uncommon	Rare	Very Rare	Not known
Infections and Infestations	Mycotic super infections				
Blood and the lymphatic system disorders		Anemia Leukopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal	
Immune system disorders		Allergic reaction Pruritus Rash Urticaria Blood eosinophilia	Anaphylactic / anaphylactoid reaction Allergic edema / angioedema (incl. laryngeal edema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)	
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia	
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts) Hallucinations	Depersonalization Psychotic reactions, (potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts)	
Nervous system disorders	Headache Dizziness	Par- and Dysesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders Tremor Vertigo Somnolence	Hypoesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; in very rare cases leading to fall with injuries, esp. in elderly) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia	Hyperesthesia	Peripheral neuropathy (that may be irreversible) and polyneuropathy
Eye disorders		Visual disturbances (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 including deafness (usually reversible)		
Cardiovascular system disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachy-arrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes* Cardiac arrest* * (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)	
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)			
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)		
Hepato-biliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life threatening liver failure (incl. fatal cases)	
Skin and subcutaneous tissue disorders				Bullous skin reactions like Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)	Drug rash with eosinophilia and systemic symptoms (DRESS), Photosensitivity reactions, Fixed drug eruptions
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Tendon rupture Arthritis Gait disturbance (caused by muscular, tendon or joint symptoms) Exacerbation of symptoms of myasthenia gravis	

Renal and urinary disorders		Dehydration (caused by diarrhea or reduced fluid intake)	Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)		
General disorders and administration site conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Edema		

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:
Common: Increased gamma-glutamyl-transferase
Uncommon: Ventricular tachyarrhythmias, Hypotension, Edema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (incl. grand mal convulsions), Hallucination, Renal impairment and renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

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

Overdose and Treatment
Symptoms: See Side Effects section.

Treatment: No specific countermeasures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Concomitant administration of charcoal with a dose of 400 mg oral moxifloxacin will reduce systemic availability of the drug by more than 80%. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.
Single doses of up to 1200 mg and multiple doses of 600 mg moxifloxacin over 10 days were administered to healthy subjects without any significant undesirable effects.

Storage Conditions
Store at temperature below 30°C. Protect from moisture.

Dosage forms and packaging available
400mg film coated tablet, 5 tablets in a blister pack.

Shelf Life:
3 years

Product Description:
Moxifcin F.C. Tablet 400mg: A pink color film coated oblong tablet, one side impressed with 'Y' 

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MXT - draft 04 Mar 2025

Date of revision: 06 Mar 2025