

**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

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**MOXIF 400**  
**(Moxifloxacin Hydrochloride Tablets)**

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**COMPOSITION**

**MOXIF-400**

Each film coated tablet contains:

Moxifloxacin Hydrochloride B.P. equivalent to Moxifloxacin 400 mg

Color: Red oxide of iron and Titanium Dioxide I.P

**DOSAGE FORM**

Film coated tablets

**INDICATIONS**

Moxifloxacin tablets are indicated for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, skin and soft tissue infections, uncomplicated urinary tract infection and pelvic inflammatory disease, in adults 18 years and above.

**POSODOLOGY AND METHOD OF ADMINISTRATION**

Posology (adults)

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

Renal/hepatic impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. 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 film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Duration of administration

Moxif 400 mg film-coated tablets should be used for the following treatment durations:

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

Moxif 400 mg film-coated tablets have been studied in clinical trials for up to 14 days treatment.

Sequential (intravenous followed by oral) therapy

In clinical studies with sequential therapy most patients switched from intravenous to oral therapy within 4 days (community-acquired pneumonia) or 6 days (complicated skin and skin structure infections). The recommended total duration of intravenous and oral treatment is 7 - 14 days for community-acquired pneumonia and 7 -21 days for complicated skin and skin structure infections

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

### **CONTRAINDICATIONS**

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- 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 > 5fold ULN.

### **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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

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  $\pm$  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 proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. 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 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.

### 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 polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop.

### 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.

### 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.

### 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 Moxif 400 mg film-coated tablets is not recommended.

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

### Patients with special cSSSi

Clinical efficacy of intravenous moxifloxacin in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Interference with biological tests

Moxifloxacin therapy may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving moxifloxacin.

#### Patients with MRSA infections

Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started.

#### Paediatric population

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

### **DRUG-INTERACTION**

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 (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

After repeated dosing in healthy volunteers, moxifloxacin increased C<sub>max</sub> 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.

### **FERTILITY, 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.

#### **Breastfeeding**

There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breast-feeding is contraindicated during moxifloxacin therapy.

#### **Fertility**

Animal studies do not indicate impairment of fertility.

### **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

### **UNDESIRABLE EFFECTS**

Adverse reactions based on all clinical trials with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:

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

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

- common ( $\geq 1/100$  to  $< 1/10$ )
- uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- very rare ( $< 1/10,000$ )

<b>System Organ Class (MedDRA)</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very Rare</b>
<b>Infections and infestations</b>	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis			
<b>Blood and lymphatic system disorders</b>		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged/INR increased		Prothrombin level increased/INR decreased Agranulocytosis
<b>Immune system disorders</b>		Allergic reaction	Anaphylaxis incl. very rarely life-threatening shock Allergic oedema / angiooedema (incl. laryngeal oedema, potentially life-threatening.	
<b>Metabolism and nutrition disorders</b>		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia
<b>Psychiatric disorders</b>		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, Hallucination	Depersonalization Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts)
<b>Nervous system disorders</b>	Headache Dizziness	Par- and Dyaesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions Disturbed attention Speech disorders	Hyperaesthesia

			Amnesia Peripheral neuropathy and polyneuropathy	
<b>Eye disorders</b>		Visual disturbances incl. diplopia and blurred vision		Transient loss of vision (especially in the course of CNS reactions)
<b>Ear and labyrinth disorders</b>			Tinnitus Hearing impairment incl. deafness (usually reversible)	
<b>Cardiac disorders</b>	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
<b>Vascular disorders</b>		Vasodilatation	Hypertension Hypotension	
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnea (including asthmatic conditions)		
<b>Gastrointestinal disorders</b>	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)	
<b>Hepatobiliary disorders</b>	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
<b>Skin and subcutaneous tissue disorders</b>		Pruritus Rash Urticaria Dry skin		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening,



<b>Musculoskeletal and connective tissue disorders</b>		Arthralgia Myalgia	Tendonitis Muscle cramp Muscle twitching Muscle weakness	Tendon rupture Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis
<b>Renal and urinary disorders</b>		Dehydration	Renal impairment (incl. increase in BUN and creatinine) Renal failure	
<b>General disorders and administration site conditions</b>		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating	Oedema	

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions.

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- disturbances in attention
- disorientation
- agitation
- nervousness
- memory impairment
- Serious disturbances in mental abilities called delirium.

## **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 *norA* or *pmrA* genes seen in certain Gram-positive bacteria.

Pharmacodynamic investigations have demonstrated that moxifloxacin exhibits a concentration dependent killing rate. Minimum bactericidal concentrations (MBC) were found to be in the range of the minimum inhibitory concentrations (MIC).

#### Effect on the intestinal flora in humans

The following changes in the intestinal flora were seen in volunteers following oral administration of moxifloxacin: *Escherichia coli*, *Bacillus* spp., *Enterococcus* spp., and *Klebsiella* spp. were reduced, as were the anaerobes *Bacteroides vulgatus*, *Bifidobacterium* spp., *Eubacterium* spp., and *Peptostreptococcus* spp.. For *Bacteroides fragilis* there was an increase. These changes returned to normal within two weeks.

#### Mechanism of resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also effect susceptibility to moxifloxacin.

In vitro resistance to moxifloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.

Cross-resistance is observed with other fluoroquinolones. However, as moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.

#### Breakpoints

EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2011):

EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2011):

<b>Organism</b>	<b>Susceptible</b>	<b>Resistant</b>
<i>Staphylococcus</i> spp.	≤ 0.5 mg/l ≥ 24 mm	> 1 mg/l < 21 mm
<i>S. pneumoniae</i>	≤ 0.5 mg/l ≥ 22 mm	> 0.5 mg/l ≥ 22 mm
<i>Streptococcus</i> Groups A, B, C, G	≤ 0.5 mg/l ≥ 18 mm	> 1 mg/l < 15 mm
<i>H. influenzae</i>	≤ 0.5 mg/l ≥ 25 mm	≤ 0.5 mg/l ≥ 25 mm
<i>M. catarrhalis</i>	≤ 0.5 mg/l ≥ 23 mm	> 0.5 mg/l < 23 mm
<i>Enterobacteriaceae</i>	≤ 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 baumannii*  
*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)<sup>+</sup>

##### Aerobic Gram-negative micro-organisms

*Enterobacter cloacae*\*  
*Escherichia coli*\*  
*Klebsiella pneumoniae*\*#  
*Klebsiella oxytoca*  
*Neisseria gonorrhoeae*\*<sup>+</sup>  
*Proteus mirabilis*\*

<u>Anaerobic micro-organisms</u> <i>Bacteroides fragilis</i> * <i>Peptostreptococcus</i> spp.*
<b>Inherently resistant organisms</b>
<u>Aerobic Gram-negative micro-organisms</u> <i>Pseudomonas aeruginosa</i>
*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

## Pharmacokinetic properties

### Absorption and Bioavailability

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

Pharmacokinetics are linear in the range of 50 - 800 mg single dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively. At steady-state the exposure within the dosing interval is approximately 30% higher than after the first dose.

### Distribution

Moxifloxacin is distributed to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 m·gh/l is observed. The steady-state volume of distribution (V<sub>ss</sub>) 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	1.6 <sup>1</sup> mg/l	1.7 <sup>1</sup>
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 <sup>2</sup> mg/l	0.8 - 1.4 <sup>2,3</sup>
Female genital tract*	10.2 <sup>4</sup> mg/kg	1.72 <sup>4</sup>

\* intravenous administration of a single 400 mg dose

<sup>1</sup> 10 h after administration

<sup>2</sup> unbound concentration

<sup>3</sup> from 3 h up to 36 h post dose

<sup>4</sup> 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<sup>2</sup>). 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<sup>2</sup>).

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

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

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

At high concentrations, moxifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT interval. Toxicological studies performed in dogs using oral doses of  $\geq 90$  mg/kg leading to plasma concentrations  $\geq 16$  mg/l caused QT prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50fold the human dose ( $> 300$  mg/kg), leading to plasma concentrations of  $\geq 200$  mg/l (more than 40fold 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 ( $\geq 60$  mg/kg) leading to plasma concentrations  $\geq 20$  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.

#### **EXPIRY DATE**

Do not use later than the date of expiry.

#### **PACKAGING INFORMATION**

MOXIF-400 is available in mono carton of 5 blister strips (each of 5 tablets)

#### **STORAGE AND HANDLING INSTRUCTIONS**

Keep in cool dry place

#### **MARKETED BY**



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**IN/MOXIF 400mg/JAN-19/04/PI**