FLOXSAFE 400 (Moxifloxacin Tablets 400 mg)

Name of the medicinal product

FLOXSAFE 400 (Moxifloxacin Tablets 400 mg) Label claim

Each Film coated tablet contains

Moxifloxacin Hydrochloride Ph.Eur. equivalent to Moxifloxacin 400 mg

Excipient(s) with known effect

Each Moxifloxacin Tablets 400 mg film-coated tablet contains 230.17 mg lactose monohydrate.

Pharmaceutical form Caplet shaped brick red colored smooth film coated tablets plain on both sides

Clinical particulars

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 (adequately diagnosed) Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia, except severe cases

Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

Moxifloxacin 400 mg film-coated tablets are indicated for the treatment of the following bacterial infections in patients of 18 years

Moxifloxacin 400 mg film-coated tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae unless moxifloxacin-resistant Neisseria gonorrhoeae can be excluded.

Moxifloxacin 400 mg film-coated tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:

Community acquired pneumonia

Complicated skin and skin structure infections

Moxifloxacin 400 mg film-coated tablets should not be used to initiate therapy for any type of skin and skin structure infection or in severe community acquired pneumonia

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

Posology and method of administration

Posology (adults) The recommended dose is one 400 mg film-coated tablet once daily.

Renal/hepatic impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis

There is insufficient data in patients with impaired liver function

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

5 -10 days

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

Duration of administration Moxifloxacin 400 mg film-coated tablets should be used for the following treatment durations:

Acute exacerbation of chronic bronchitis Community acquired pneumonia

Sequential (intravenous followed by oral) therapy

Acute bacterial sinusitis 7 days Mild to moderate pelvic inflammatory disease 14 days

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

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 listed in
- 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

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

 $\underline{Prolongation\ of\ QTc\ interval\ and\ potentially\ QTc\ -prolongation\ -related\ clinical\ conditions}$

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 $de\ pointes)\ and\ cardiac\ arrest\ .\ The\ magnitude\ of\ QT\ prolongation\ may\ increase\ with\ increasing\ concentrations\ of\ the\ drug.\ Therefore,$ e 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

Inypersensitivity 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.

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 StevensJohnson 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 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 selfinjurious 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 antibioticassociated 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 moxifloxacintreated 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 glucose6phosphate 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 galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should

Patients with pelvic inflammatory disease

For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with Moxifloxacin 400 mg film-coated tablets is not recommended.

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae. Therefore in such cases empirical mostifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless mostifloxacin-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

contraindicated

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 moxifloxacing 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

Interaction with other medicinal products and other forms of interaction Interactions with medicinal products

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

certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine) certain

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

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 thiazidetype 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 mended (except for overdose cases.

 $After \ repeated \ dosing \ in \ healthy \ volunteers, \ moxifloxacin \ increased \ C_{max \ of} \ digoxin \ by \ approximately \ 30\% \ without \ affecting \ AUC \ or \ approximately \ app$ 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 itraconazol

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 and the safety of th used in pregnant women Breastfeeding

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

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones

There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in

Effects on ability to drive and use machine

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.

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 ($\ge 1/100 \text{ to} < 1/10$)

uncommon (≥ 1/1,000 to < 1/100)

rare ($\geq 1/10,000 \text{ to} \leq 1/1,000$) very rare (< 1/10,000)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis			
Blood and lymphatic system disorders		Anaemia Leucopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged/INR increased		Prothrombin level increased/INR decreased Agranulocytosis
Immune system disorders		Allergic reaction	Anaphylaxis incl. Very rarely lifethreatening shock Allergic oedema / angiooedema (incl. laryngeal oedema, potentially lifethreatening,	
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 selfinjurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, Hallucination	Depersonalization Psychotic reactions (potentially culminating in selfinjurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts,
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 Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye disorders		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions,		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	
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)	ypotension	

Dimensions: 240 x 450 mm

Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudomembranous colitis, in very rare cases associated with lifethreatening complications,	
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gammaglutamyltransferase 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 StevensJohnson syndrome or toxic epidermal necrolysis (potentially lifethreatening,
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
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		

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

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: I01MA14

Mechanism of action

Moxifloxacin has in vitro activity against a wide range of Gram-positive and Gramnegative 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-

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 moxifloxacir

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

Organism	Susceptible	Resistant	
Staphylococcus spp.	≤ 0.5 mg/l	> 1 mg/l	
	≥ 24 mm	< 21 mm	
S. pneumoniae	≤ 0.5 mg/l	> 0.5 mg/l	
	≥ 22 mm	≥ 22 mm	
Streptococcus Groups A, B, C, G	≤ 0.5 mg/l	> 1 mg/l	
	≥ 18 mm	< 15 mm	
H. influenzae	≤ 0.5 mg/l	$\leq 0.5 \text{ mg/l}$	
	≥ 25 mm	≥ 25 mm	
M. catarrhalis	≤ 0.5 mg/l	> 0.5 mg/l	
	≥ 23 mm	< 23 mm	
Enterobacteriaceae	≤ 0.5 mg/l	> 1 mg/l	
	\geq 20 mm	< 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 ch that utility of the agent in at least some types of infecti-

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

Aerobic Gram-egative micro-organisms

Haemophilus influenzae

Haemophilus parainfluenzae*

Legionella pneumophila Moraxella (Branhamella) catarrhalis*

Anaerobic micro-organisms

Fusobacterium spp. Prevotella spp.

"Other" micro-organisms

Chlamydophila (Chlamydia) pneumoniae Chlamvdia 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.3 Inherently resistant organisms

Aerobic Gram-egative 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

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 steadystate (400 mg once daily) were 3.2 and 0.6 mg/l, respectively. At steadystate the exposure within the dosing interval is approximately 30% higher than after the first dose.

Moxifloxacin is distributed to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 m·gh/l is observed.

The steadystate 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 alb

The following peak concentrations (geometric mean) were observed following administration of a single oral dose of 400 mg

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	1.0 ² mg/l	0.8 -1.4 ^{2,3}
Female genital tract*	10.24 mg/kg	1.724

intravenous administration of a single 400 mg dose

1 10 h after administration

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 sulphocompound (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

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.

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine

clearance > 20 ml/min/1.73 m², 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 m²).

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 On the basis of the pharmacokinetic studies carried out so far in patients with five failure (Child rugh A, B), it's 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 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 noncarcinogenic in an initiation promotion study in rats.

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

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

Ouinolones 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

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

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 Pharmaceutical particulars

an atrophy of the retina

Lactose monohydrate, Povidone, Lactose anhydrous, Croscarmellose sodium, Colloidal silicon Dioxide, Magnesium Stearate, Coating: Hypromellose, Polyethylene Glycol, Titanium Dioxide & Iron oxide Red.

Incompatibilities Not applicable

Do not store above 30°C. Protect from light and moisture. Keep out of reach of children.

Nature and contents of container PVC/PVDC-Alu blister of 5 tablets and 10 tablets. Packs containing 1 x 5's, 3 x 5's and 3 x 10's Not all pack sizes may be marketed.

Manufactured by:

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