

MAXLOX
(MOXIFLOXACIN)

400mg/250 mL

I.V. Infusion

WARNING

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded.

COMPOSITION

Each 250ml contains:
Moxifloxacin as HCl (U.S.P.) 400mg

THERAPEUTIC INDICATIONS

Moxifloxacin is indicated for the treatment of:

- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)

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.

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

DOSAGE AND ADMINISTRATION

The recommended dose is 400 mg moxifloxacin, infused once daily.

Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400 mg tablets, when clinically indicated.

In clinical studies most patients switched to oral therapy within 4 days (CAP) or 6 days (cSSSI). The recommended total duration of intravenous and oral treatment is 7 - 14 days for CAP and 7 - 21 days for cSSSI.

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. hemodialysis 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 growing adolescents. Efficacy and safety of moxifloxacin in children and adolescents have not been established.

Method of administration

For intravenous use; constant infusion over 60 minutes.

If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions.

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 hypokalemia
- 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 medicinal products 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 use of moxifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment

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

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

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 ischaemia) 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 medications that can reduce potassium levels.

Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia.

Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.

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.

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 Generalized 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 the symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, moxifloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or AGEP with the use of moxifloxacin, treatment with moxifloxacin must not be restarted in this patient at any time.

Patients predisposed to seizures

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

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Moxifloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of a potentially irreversible condition.

Psychiatric reactions

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

Antibiotic-associated diarrhoea incl. colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of broad-spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to

occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or 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, Behet'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 dyspnea, 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. Cases of hypoglycemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitivity reactions

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

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.

Peri-arterial tissue inflammation

Moxifloxacin solution for infusion is for intravenous administration only. Intra-arterial administration should be avoided since preclinical studies demonstrated peri-arterial tissue inflammation following infusion by this route.

Patients with special cSSSI

Clinical efficacy of 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 INTERACTIONS

Interactions with medicinal products

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

- 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 antidepressants
- 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, sucralate 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 medicinal products is not recommended (except for overdose cases).

After repeated dosing in healthy volunteers, moxifloxacin increased C_{max} 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 hyperglycemia. 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 normalized ratio) disorder. A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole.

In vitro studies with human cytochrome P450 enzymes support these findings. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.

Interaction with food

Moxifloxacin has no clinically relevant interaction with food including dairy products.

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, breastfeeding 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.

ADVERSE DRUG REACTIONS

Adverse reactions observed in clinical trials and derived from post-marketing reports with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:

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

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

- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis				
Blood and lymphatic system disorders		Anaemia		Prothrombin level increased / INR decreased	
		Leucopenia(s)		Agranulocytosis	
		Neutropenia		Pancytopenia	
		Thrombocytopenia			
		Thrombocythemia			
		Blood eosinophilia			
		Prothrombin time prolonged / INR increased			
Immune System Disorders		Allergic reaction	Anaphylaxis incl. very rarely life-threatening shock.		
			Allergic oedema / angioedema (incl. laryngeal oedema, potentially life-threatening)		

Endocrine disorders				Syndromes of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycemia	Hypoglycemia	
			Hyperuricemia	Hypoglycemic coma	
Psychiatric disorders*		Anxiety reactions	Emotional lability	Depersonalization	
		Psychomotor hyperactivity / agitation	Depression (in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideations/ thoughts, or suicide attempts,	Psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts, or suicide attempts,	
				Hallucination	
				Delirium	
Nervous System Disorders*	Headache	Para- and Dysesthesia	Hypoesthesia	Hyperesthesia	
	Dizziness	Taste disorders (incl. ageusia in very rare cases)	Smell disorders (incl. anosmia)		
		Confusion and disorientation	Abnormal dreams		
		Sleep disorders (predominantly insomnia)	Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo)		
		Tremor	Seizures incl. grand mal convulsions		

		Vertigo	Disturbed attention		
		Somnolence	Speech disorders		
			Amnesia		
			Peripheral neuropathy and polyneuropathy		
Eye Disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions,	Photophobia	Transient loss of vision (especially in the course of CNS reactions ,	
				Uveitis and bilateral acute iris transillumination	
Ear and Labyrinth Disorders*			Tinnitus		
			Hearing impairment incl. deafness (usually reversible)		
Cardiac Disorders**	QT prolongation in patients with hypokalemia	QT prolongation	Ventricular tachyarrhythmias	Unspecified arrhythmias	
		Palpitations	Syncope (i.e., acute and short lasting loss of consciousness)	Torsade Pointes	
		Tachycardia		Cardiac arrest	
		Atrial fibrillation			
		Angina pectoris			
Vascular Disorders**		Vasodilation	Hypertension	Vasculitis	
			Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Dyspnea (including asthmatic conditions)			

Gastrointestinal Disorders	Nausea	Decreased appetite and food intake	Dysphagia		
	Vomiting	Constipation	Stomatitis		
	Gastrointestinal and abdominal pains	Dyspepsia	Antibiotic associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications,		
	Diarrhea	Flatulence			
		Gastritis			
		Increased amylase			
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase)	Jaundice	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases,	
		Increased bilirubin	Hepatitis (predominantly cholestatic)		
		Increased gamma-glutamyl-transferase			
		Increase in blood alkaline phosphatase			
Skin and Subcutaneous Tissue Disorders		Pruritus		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening)	Acute Generalized Exanthematous Pustulosis (AGEP)
		Rash			
		Urticaria			
		Dry skin			
Musculoskeletal and		Arthralgia	Tendonitis	Tendon rupture	Rhabdomyolysis

connective Tissue Disorders*		Myalgia	Muscle cramp	Arthritis	
			Muscle twitching	Muscle rigidity	
			Muscle weakness	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)	Oedema		
		Painful conditions (incl. pain in back, chest, pelvic and extremities)			
		Sweating			

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

**Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/ incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anemia, photosensitivity reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

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 medicinal product 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: J01 MA 14

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 penicillin, 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 affect susceptibility to moxifloxacin.

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

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

Breakpoints

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

Organism	Susceptible	Resistant
<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
<u>Aerobic Gram-positive micro-organisms</u>
<i>Gardnerella vaginalis</i>
<i>Staphylococcus aureus</i> * (methicillin-susceptible)
<i>Streptococcus agalactiae</i> (Group B)
<i>Streptococcus milleri</i> group* (<i>S. anginosus</i> , <i>S. constellatus</i> and <i>S. intermedius</i>)
<i>Streptococcus pneumoniae</i> *
<i>Streptococcus pyogenes</i> * (Group A)
<i>Streptococcus viridans</i> group (<i>S. viridans</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>S. sanguinis</i> , <i>S. salivarius</i> , <i>S. thermophilus</i>)
<u>Aerobic Gram-negative micro-organisms</u>
<i>Acinetobacter baumannii</i>
<i>Haemophilus influenzae</i> *
<i>Haemophilus parainfluenzae</i> *
<i>Legionella pneumophila</i>
<i>Moraxella (Branhamella) catarrhalis</i> *
<u>Anaerobic micro-organisms</u>
<i>Fusobacterium</i> spp.
<i>Prevotella</i> spp.
"Other" micro-organisms
<i>Chlamydia (Chlamydia) pneumoniae</i> *
<i>Chlamydia trachomatis</i> *
<i>Coxiella burnetii</i>
<i>Mycoplasma genitalium</i>
<i>Mycoplasma hominis</i>
<i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
<u>Aerobic Gram-positive micro-organisms</u>
<i>Enterococcus faecalis</i> *
<i>Enterococcus faecium</i> *
<i>Staphylococcus aureus</i> (methicillin-resistant)*
<u>Aerobic Gram-negative micro-organisms</u>
<i>Enterobacter cloacae</i> *
<i>Escherichia coli</i> **
<i>Klebsiella pneumoniae</i> **
<i>Klebsiella oxytoca</i>
<i>Neisseria gonorrhoeae</i> **
<i>Proteus mirabilis</i> *
<u>Anaerobic micro-organisms</u>

<i>Bacteroides fragilis</i> *
<i>Peptostreptococcus</i> spp.*
Inherently resistant organisms
<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 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively. At steady-state the exposure within the dosing interval is approximately 30% higher than after the first dose.

Distribution

Moxifloxacin is distributed to extravascular spaces rapidly; after a dose of 400 mg an AUC of 35 m·gh/l is observed. The steady-state volume of distribution (Vss) is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

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

Tissue	Concentration	Site: Plasma ratio
Plasma	3.1 mg/l	-
Saliva	3.6 mg/l	0.75 - 1.3
Blister fluid	1.6 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}
Female genital tract*	10.2 ⁴ mg/kg	1.72 ⁴

* intravenous administration of a single 400 mg dose

¹ 10 h after administration

² unbound concentration

³ from 3 h up to 36 h post dose

⁴ at the end of infusion

Biotransformation

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

In clinical Phase I and *in vitro* studies no metabolic pharmacokinetic interactions with other medicinal products 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 feces (approximately 25% of unchanged drug, approximately 36% for M1, and no recovery for M2) totaled 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 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).

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 ≥ 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, non-fatal ventricular arrhythmias were seen.

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

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

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in fetuses 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.

PRESENTATION

Maxlox 400mg/250ml injection is available in 250ml glass vial.

INSTRUCTIONS

- Injection should not be used if container is leaking, solution is cloudy or it contains un-dissolved particle(s).
- To be sold on prescription of a registered medical practitioner only.
- Store below 25°C.
- Keep out of sight and reach of children.
- Protect from sunlight, moisture and heat.
-

REGISTRATION NUMBER

Maxlox Injection: 060632
Manufacturing License No.: 000586

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Product Complies Manufacturer's Specs.

Manufactured by:

Searle IV Solutions (Pvt.) Limited.

1.5 km, Manga Raiwind Road, Manga Mandi, Distt. Lahore - Pakistan.

Marketed by:

The Searle Company Limited,

One IBL Centre, 2nd Floor, Plot # 1, Block 7 & 8,

D.M.C.H.S, Tipu Sultan Road, Off Shahra-e-Faisal,

Karachi - Pakistan.

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