

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: J01MA14

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 bicyclicamine 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.

Break points

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

Aerobic Gram-positive micro-organisms
<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>)
Aerobic Gram-negative micro-organisms
<i>Acinetobacter baumannii</i>
<i>Haemophilus influenzae</i> *
<i>Haemophilus parainfluenzae</i> *
<i>Legionella pneumophila</i>
<i>Moraxella (Branhamella) catarrhalis</i> *
Anaerobic micro-organisms
<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
Aerobic Gram-positive micro-organisms
<i>Enterococcus faecalis</i> *
<i>Enterococcus faecium</i> *
<i>Staphylococcus aureus</i> (methicillin-resistant)+
Aerobic Gram-negative micro-organisms
<i>Enterobacter cloacae</i> *
<i>Escherichia coli</i> *
<i>Klebsiella pneumoniae</i> *#
<i>Klebsiella oxytoca</i>
<i>Neisseria gonorrhoeae</i> *+
<i>Proteus mirabilis</i> *

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

Distribution

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 (*V*_{ss}) 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 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.

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 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 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.

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

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

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

Pharmaceutical particulars

List of excipients

Lactose monohydrate, Povidone, Lactose anhydrous, Croscarmellose sodium, Colloidal silicon Dioxide, Magnesium Stearate,

Coating: Hypromellose, Polyethylene Glycol, Titanium Dioxide & Iron oxide Red.

Incompatibilities

Not applicable.

Storage

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:

MSN LABORATORIES PRIVATE LIMITED (Formulations Division)

Plot No. 42, ANRICH Industrial Estate,

Bollaram, Sangareddy Dist – 502 325,

Telangana, India.