Moxifloxacin

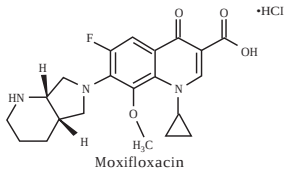
XIFLOX

1.6 mg/mL (400 mg/250 mL)

Solution for Injection (I.V. Infusion)
Antibacterial (Fluoroquinolone)

DESCRIPTION

Moxifloxacin (XIFLOX) IV is a synthetic broad-spectrum antibacterial agent. Chemically, moxifloxacin is a fluoroquinolone and is available as a monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8 diazabicyclo[4.3.0]non-8-yl]-6-flouro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid. The molecular formula is $C_{21}H_{24}FN_3O_4$*HCl and the structural formula is:



Moxifloxacin

FORMULATION

Each mL contains:
Moxifloxacin (as hydrochloride)…1.6 mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Moxifloxacin is bactericidal against a wide range of gram positive and gram negative organisms. Such activity arises through the inhibition of DNA gyrase (topoisomerase II) and topoisomerase IV, which bacteria require for DNA replication, transcription, repair, and recombination. Moxifloxacin contains the C8-methoxy moiety that augments its antibacterial activity and reduces the possibility of gram–positive mutations. Because the 8-fluroquinolones use a different mechanism of action than the aminoglycosides, beta-lactams, macrolides, or tetracyclines, there has been no cross resistance between the quinolones and these antimicrobial agents.

Microbiology:

Spectrum of moxifloxacin is broad and it is active against most strains of the following micro-organisms in both *in vitro* and *in vivo*.

Aerobic Gram-positive micro-organisms:
Staphylococcus aureus (including methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes
Streptococcus anginosus
Streptococcus constellatus
Gardnerella vaginalis
Streptococcus milleri
Streptococcus mitior
Streptococcus agalactiae
Streptococcus dysgalactiae
Staphylococcus cohnii
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus simulans
Corynebacterium diphtheriae
*Enterococcus faecalis** (Vancomycin, gentamicin susceptible strains only)

Aerobic Gram-negative micro-organisms:
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis (including -lactamase negative and positive strains)
Enterobacter cloacae
Escherichia coli
Proteus mirabilis
Klebsiella pneumoniae
Bordetella pertussis
Klebsiella oxytoca
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter intermedius
Enterobacter sakazakii
Proteus vulgaris
Morganella morganii
Providencia rettgeri
Providencia stuartii

Atypicals
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae
Mycoplasma hominis
Mycoplasma genitalum
Legionella pneumophila
Coxiella burnetti

Anaerobic micro-organisms:
Bacteroides distasonis
Bacteroides eggerthii
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Fusobacterium spp.
Peptostreptococcus spp.
Porphyromonas spp.
Porphyromonas anaerobius Porphyromonas asaccharolyticus Porphyromonas magnus
Prevotella spp.
Propionibacterium spp.
Clostridium perfringens
Clostridium ramosum

Pharmacokinetics

Absorption

After a single 400mg intravenous 1 hour infusion peak concentrations of approximately 4.1mg/L were reached in the plasma at the end of infusion which corresponds to a mean increase of approximately 26% relative to the oral application. Following multiple intravenous dosing (1 hour infusion), peak and trough plasma concentrations at steady state (400mg once daily) were between 4.1 to 5.9mg/L and 0.43 to 0.84mg/L respectively.

Distribution

Moxifloxacin is approximately 30-50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, subcutaneous tissue, skeletal muscle, and abdominal tissues and fluids following intravenous administration of 400mg

Metabolism

Approximately 52% of an intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the feces. While glucuronide conjugate (M2) accounts for approximately 14% of the dose which is excreted exclusively in the urine. Peak plasma concentration of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Excretion

Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400mg dose ranges from 179 to 246mL/min. Renal clearance amounted to about 24 - 53mL/min suggesting partial tubular reabsorption of the medicine from the kidneys. Approximately 45% of intravenous dose of moxifloxacin is excreted as unchanged drug (20% is excreted in the urine and 25% in the feces).

THERAPEUTIC INDICATIONS

Moxifloxacin (XIFLOX) IV is indicated for the treatment of adults (>18 years of age) with mild, moderate and severe infections caused by susceptible strains of micro-organisms in the conditions listed below:

- Acute bacterial sinusitis.
- Acute bacterial exacerbation of chronic bronchitis.
- Community acquired pneumonia.
- Uncomplicated skin and skin structure infections.
- Complicated intra-abdominal infections (including polymicrobial infections such as abscesses).
- Complicated skin and skin structure infections (including diabetic foot infections).

DOSAGE AND ADMINISTRATION

The dose of Moxifloxacin (XIFLOX) IV is 400 mg/250 mL as intravenous infusion once every 24 hours. The duration of treatment should be determined by the severity of the indication or clinical response. The recommended duration of treatment for the indication being treated should not be exceeded.

Infection	Daily Dose	Duration
Acute bacterial sinusitis	400mg	10 days
Acute bacterial exacerbation of chronic bronchitis	400mg	5 days
Community acquired pneumonia	400mg	7 – 14 days
Uncomplicated skin and skin structure infections	400mg	7 days
Complicated skin and skin structure infections	400mg	7 – 21 days
Complicated intra-abdominal infection	400mg	5-14 days

Moxifloxacin (XIFLOX) IV can be administered intravenously for the entire treatment duration. Alternatively, therapy may be initial intravenous administration, followed by oral administration when clinically indicated.

Method of Administration

Moxifloxacin (XIFLOX) IV should be administered by intravenous infusion only over a period of 60 minutes. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal or subcutaneous administration.
Additives or other medications should not be added to Moxifloxacin (XIFLOX) IV or infused simultaneously through the same intravenous line.

CAUTION: Rapid or bolus intravenous infusion must be avoided.

ADVERSE EFFECTS
Following are the adverse effects reported with moxifloxacin *Common:* Mycotic superinfections, headache, dizziness, QT prolongation in patients with hypokalemia, nausea, vomiting, gastrointestinal and abdominal pains, diarrhea, increase in transaminases, injection and infusion site reactions.

Uncommon:
Anemia, leukopenia, neutropenia, thrombocytopenia, thrombocythemia, prothrombin time prolonged/INR increased, allergic reaction, pruritus, rash, urticaria, blood eosinophilia, hyperlipidemia, anxiety reactions, psychomotor hyperactivity/agitation, par- and dysesthesia, taste disorders (incl. ageusia in very rare cases), confusion and disorientation, sleep disorders, tremor, vertigo, somnolence, visual disturbances (esp in the course of CNS reactions), QT prolongation, palpitations tachycardia, vasodilatation, dyspnea (including asthmatic conditions), anorexia, constipation, dyspepsia, flatulence, gastroenteritis (excl. erosive gastroenteritis), increased amylase, hepatic impairment (incl. LDH increase), increased bilirubin, increased gamma-glutamyl-transferase, increase in blood alkaline phosphatase, arthralgia, myalgia, dehydration (caused by diarrhea or reduced fluid intake), feeling unwell, unspecific pain, sweating, infusion site (thrombo-) phlebitis.

Rare:
Thromboplastin level abnormal, anaphylactic/anaphylactoid reaction, allergic edema/angioedema (incl. laryngeal edema, potentially life threatening), hyperglycemia, hyperuricemia, emotional lability, depression (in very rare cases potentially culminating in self-endangering behaviour), hallucinations, hypoesthesia, smell disorders (incl. anosmia), abnormal dreams, disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; in very rare cases leading to fall with injuries, esp. in elderly) seizures of various clinical manifesta-tions (incl. grand mal convulsions), disturbed attention, speech disorders, amnesia, tinnitus, ventricular tachyarrhythmias, syncope, hypertension, hypotension, dysphagia, stomatitis, antibiotic associated colitis (in very rare cases associated with life threatening complications), jaundice, hepatitis (predominantly cholestatic), tendonitis, increased muscle tone and cramping, renal impairment, renal failure (due to dehydration esp. in elderly with pre-existing renal disorders), edema.

Very Rare:
Prothrombin level increased/INR decreased, prothrombin level/INR abnormal, anaphylactic/anaphylactoid shock (potentially life threatening), psychiatric disorders, depersonalization, psychotic reactions (potentially culminating in self-endangering behaviour), hyperesthesia, unspecified arrhythmias, torsade de Pointes, cardiac arrest (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia), fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases), bullous skin reactions like Stevens-Johnson-Syndrome or toxic epidermal necrolysis (potentially life threatening), tendon rupture, arthritis gait disturbance (caused by muscular, tendon or joint symptoms) exacerbation of symptoms of myasthenia gravis.

CONTRAINDICATIONS
Moxifloxacin is contraindicated in
- Patients with a history of hypersensitivity to moxifloxacin or any member of the quinolones class of antimicrobial agents.
- Pediatric patients, adolescents (less than 18 years of age).
- Pregnant and lactating women.
- Moxifloxacin should be avoided in patients with known prolongation of the QT interval, with uncorrected hypokalemia and patients receiving Class IA (quinidine, procainamide) and Class III (amiodarone, sotalol) antiarrhythmic agents.

PRECAUTIONS
- Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as bradycardia or acute myocardial ischemia.
- Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with moxifloxacin must be discontinued, medical treatment (e.g. treatment for shock) is required.
- As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders or in the presence of other risk factors that may predispose to seizures or lower the threshold.
- Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.
- Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.
- Antibiotic associated colitis has been reported with the use of broad-spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhea in association with the use of moxifloxacin. If antibiotic associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.
- Quinolones may cause central nervous system (CNS) events, including nervousness, agitation, insomnia, anxiety, nightmares or paranoia.
- As the magnitude of QT prolongation may increase with increasing concentrations of the drug, the recommended dose and the infusion rate (400mg within 60 minutes) should not be exceeded.
- Moxifloxacin should be used with caution in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.
- Tendon inflammation and rupture may occur with quinolone therapy, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment and rest the affected limbs.
- Quinolones have been shown to cause photosensitivity reactions in patients. Patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.
- Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis can occur due to use of moxifloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.
- In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account.

Drug Interactions
Anticoagulants:
Concomitant administration of anticoagulants with moxifloxacin may cause an increase in the anticoagulant activity. Therefore, INR monitoring should be performed and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Nonsteroidal anti-inflammatory drugs (NSAIDs):
The concomitant administration of an NSAID with a quinolone may increase the risks of CNS stimulation and convulsions.

Cisapride, erythromycin, anti-psychotics and *tricyclic antidepressants*
An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, anti-psychotics and tricyclic antidepressants cannot be excluded; therefore moxifloxacin should be used with caution when given concurrently with these drugs.

Morphine
Parental administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased Cmax (17%).

Atenolol
The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Digoxin:
The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin and vice versa. After repeated dosing in healthy volunteers, moxifloxacin increased Cmax of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

OVERDOSAGE
In the event of overdosage it is recommended that appropriate supportive care including ECG measurements should be instituted as dictated by the patient's clinical status. The use of charcoal early after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of overdosage.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Do not refrigerate or freeze.
Protect from light.
Infusion vial should be removed from the box only immediately before use.

The expiration date refers to the product correctly stored at the required conditions.

AVAILABILITY
Moxifloxacin (XIFLOX) IV 400 mg/250 mL is available USP Type II clear glass vial of 250mL, box of 1's.

Keep out of reach of children.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any Adverse Drug Reaction.

REGISTRATION NUMBER: DR-XY44737

DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION:
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Renewal: 03 August, 2020

DATE OF REVISION OF PACKAGING INSERT: 01 October, 2020

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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