Moxifloxacin

Xiflox®

℞

400mg Film-Coated Tablet
Antibacterial (Fluoroquinolone)

PRODUCT DESCRIPTION
Moxifloxacin (Xiflox) 400mg film coated tablet is available as pink oblong shaped, film coated tablet, engraved "GETZ" on one side and break line on other side.

FORMULATION
Each film-coated tablet contains:
Moxifloxacin (as hydrochloride), Ph. Eur. … 400mg

CLINICAL PHARMACOLOGY
Pharmacodynamics
Moxifloxacin is a 8-methoxy-fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. Moxifloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, anaerobes, acid fast bacteria and atypicals e.g. *Chlamydia spp. Mycoplasma spp.* and *Legionela spp.*
The bactericidal action results from the interference with topoisomerase II and IV. Topoisomerase are essential enzymes which control DNA topology and assist in DNA replication, repair and transcription.
Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations.
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 do the aminoglycosides, beta-lactams, macrolides, or tetracyclines, there has been no cross resistance between the quinolones and these antimicrobial agents.

MICROBIOLOGY:
Aerobic Gram-positive micro-organisms:
Susceptible
Gardnerella vaginalis, Staphylococcus aureus (methicillin-susceptible strains), *Streptococcus agalactiae, Streptococcus milleri* group (*S. anginosus, S. constellatus and S. intermedius), Streptococcus pneumoniae, Streptococcus pyogenes* (Group A), *Streptococcus viridans* group *(S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus, S. constellatus), Streptococcus dysgalactiae, Coagulase negative Staphylococci (S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans) methicillin susceptible strains.*
Intermediate
Enterococcus faecalis (Vancomycin, Gentamycin, susceptible strains only), *Entercoccus avium, Enterococcus faecium.*
Resistant
Staphylococcus aureus (methicillin/ ofloxacin resistant strains), Coagulase negative Staphylococci *(S. cohnii, S. epidermidis). S. haemolyticus, S. hominis, S. saprophyticus, S. simulans)* methicillin resistant strains.

Aerobic Gram-negative micro-organisms:
Susceptible
Haemophilus influenzae (including β lactamase negative and positive strains), *Haemophilus parainfluenzae, Moraxella catarrhalis* (including β lactamase negative and positive strains, *Bordetella pertussis, Legionella pneumophila, Acinetobacter baumanii, Proteus vulgaris*
Intermediate
Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Citrobacter freundii, Enterobacter species (E. aerogenes, E. intermedius, E. sakazaki), Enterobacter cloacae, Pantoea agglomerans, Pseudomonas fluorescens, Burkholderia cepacia, Stenotrophomonas maltophilia, Proteus mirabilis, Morganella morganii, Neisseria gonorrhea, Providence species *(P. rettgeri, P. stuartii)*
Resistant
Pseudomonas aeruginosa

Anaerobic micro-organisms:
Susceptible
Fusobacterium spp., Porphyromonas spp., Prevotella spp., Propionibacterium spp.
Intermediate
Bacteroides sp (B. fragilis, B. distasoni, B. thetaiotaomicron, B. ovatus, B. uniformis, B. vulgaris), Peptostreptococcus spp., Clostridium sp

Atypicals:
Susceptible
Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma pneumoniae, Coxiella burnetii

PHARMACOKINETICS
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 - 1200 mg single dose and up to 600 mg once daily dosing over 10 days.
Following a 400 mg oral dose peak concentrations of 3.1 mg/L are reached within 0.5 - 4 h post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2mg/L and 0.6 mg/L, respectively.
Distribution
Moxifloxacin is distributed very rapidly to extravascular spaces. Exposure to drug in terms of AUC (AUC_{norm} = 6kg.h/L) is high with steady-state volume of distribution (V_{ss}) of approximately 2 L/kg. In saliva peak concentrations higher than those of plasma maybe reached. *In vitro* and *ex vivo* experiments over a range of 0.02 to 2mg/L shows the determination of protein binding of approximately 45% (independent of the concentration of the drug). Moxifloxacin is mainly bound to serum albumin. Due to this low value it shows high free peak concentration > 10x MIC are observed. Moxifloxacin reaches high concentrations in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissues), the sinuses (maxillary and ethmoid sinus, nasal polyps) and inflamed lesions (catharide blister fluid) where total concentrations exceeding those of the plasma concentrations are reached. High free drug concentrations are measured in interstitial body water (saliva, intramuscular, subcutaneous). In addition, high drug concentrations were detected in abdominal tissues and fluids and female genital tract.
The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400mg moxifloxacin.
Metabolism
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.

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.
Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.
Mass balance of the mother compound and Phase II metabolites of moxifloxacin yielded an almost complete recovery of approximately 96% - 98% independent from the route of administration with no indication of oxidative metabolism.

Special Population
Geriatric patients
Pharmacokinetics of moxifloxacin are not affected by age.
Gender
Drug absorption of Moxifloxacin is not affected by gender.

THERAPEUTIC INDICATIONS
Moxifloxacin (Xiflox) tablets are indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin.
- Respiratory tract infections:
  - Acute bacterial sinusitis.
  - Acute exacerbations of chronic bronchitis.
  - Community acquired pneumonia, including CAP caused by multi-drug resistant strains.
- Uncomplicated skin and skin structure infections.
- Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis).
- Complicated skin and skin structure infections (including diabetic foot infections).
- Complicated intraabdominal infections including polymicrobial infections such as abscesses.

DOSAGE AND ADMINISTRATION
The usual adult dose of Moxifloxacin (Xiflox) is 400mg once every 24 hours. The duration of therapy depends on the type and severity of infection as described in the table below.
The film-coated tablet should be swallowed whole with sufficient liquid and maybe taken independent of meals.

Infection	Daily Dose	Duration
Acute bacterial sinusitis	400mg	7 days
Acute bacterial exacerbations of chronic bronchitis	400mg	5 days
Community acquired pneumonia	400mg	10 days
Uncomplicated skin and skin structure infections	400mg	7 days
Complicated skin and skin structure infections	400mg	7 – 21 days
Uncomplicated pelvic inflammatory disease	400mg	14 days
Complicated intraabdominal infections	400mg	5 – 14 days

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

Missed dose
If a dose is missed, it should be taken as soon as the patient remembers on the same day. Double doses should not be taken to compensate for a missed dose.

Special Populations
Geriatric patients
No adjustment of dosage is required in elderly.

Ethnic differences
No adjustment of dosage is required in ethnic groups.

Patients with hepatic impairment
No adjustment of dosage is required in patients with impaired liver function.

Patients with renal impairment
No adjustment of dosage is required in patients with impaired renal function.

ADVERSE REACTIONS
Moxifloxacin is usually well tolerated. Most adverse reactions are mild to moderate. The most common adverse reactions are nausea and diarrhea.
- Infection and infestations
Common: Myotic superinfections
- Blood and Lymphatic system disorders
Uncommon: Anemia, Leukopenia, Neutropenia, Thrombocytopenia, Thrombocytothemia, Prothrombin, time prolonged / INR increased.
Rare: Thromboplastin level abnormal
Very rare: Prothrombin level increased / INR decreased Prothrombin level / INR abnormal
- Immune system disorders
Uncommon: Allergic reaction, Pruritus, Rash, Urticaria, Blood eosinophilia
Rare: Anaphylactic / anaphylactoid reaction, Allergic edema / angioedema
Very rare: Anaphylactic / anaphylactoid shock
- Metabolism and nutrition disorders
Uncommon: Hyperlipidemia
Rare: Hyperglycemia, Hyperuricemia
Very rare: Hypoglycemia
- Psychiatric disorders
Uncommon: Anxiety reactions, Psychomotor hyperactivity/ agitation
Rare: Emotional liability, Depression, Hallucinations
Very rare: Depersonalization, Psychotic reactions
- Nervous system disorders
Common: Headache, Dizziness
Uncommon: Paresthesia and dysesthesia taste disorders (including ageusia in very rare cases), Confusion and disorientation, Sleep disorders, Tremor, Vertigo , Somnolence
Rare: Hypoesthesia, Smell disorders (including anosmia), Abnormal dreams, Disturbed coordination (including gait disturbances, especially due to dizziness or vertigo; in very rare cases leading to fall with injuries, especially in elderly), Seizures of various clinical manifestations (including grand malconvulsions), Disturbed attention, Speech disorders, Amnesia, Peripheral neuropathy and polyneuropathy.

210 mm

130 mm

Very rare: Hyperesthesia
- Eye disorders
Uncommon: Visual disturbances (especially in the course of CNS reactions)
Very rare: Transient loss of vision (especially in the course of CNS reactions)
- Ear and Labyrinth disorders
Rare: Tinnitus, Hearing impairment including deafness (usually reversible)
- Cardiovascular system disorders
Common**:** QT prolongation in patients with hypokalaemia
Uncommon: QT prolongation , Palpitations, Tachycardia, Vasodilation
Rare: Ventricular tachyarrythmias, Syncope, Hypertension, Hypotension
Very rare: Unspecified arrhythmias, Torsades de Pointes, Cardiac arrest (especially in patients with severe underlying proarythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)
- Respiratory, thoracic, and mediastinal disorders
Uncommon: Dyspnea (including asthmatic conditions)
- Gastrointestinal disorders
Common: Nausea, Vomiting, Gastrointestinal and abdominal pains, Diarrhea
Uncommon: Decreased appetite and food intake, Constipation, Dyspepsia, Flatulence, Gastroenteritis (excluding erosive gastroenteritis), Increased amylase
Rare: Dysphagia, Stomatitis, Antibiotic associated colitis
- Hepato-biliary disorders
Common: Increase in transaminases
Uncommon: Hepatic impairment (including LDH increase), Increased bilirubin, Increase gamma-glutamyl-transferase, Increase in blood alkaline phosphatase
Rare: Jaundice, Hepatitis (predominantly cholestatic)
Very rare: Fulminant hepatitis
- Skin and subcutaneous tissue disorders
Very rare: Bullous skin reactions like Stevens Johnson Syndrome or Toxic Epidermal Necrolysis
- Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, Myalgia
Rare: Tendonitis, Increased muscle tone and cramping, Muscular weakness
Very rare: Tendon rupture, Arthritis, Gait disturbances (caused by muscular, tendon, or joint symptoms), Exacerbation of symptoms of myasthenia gravis
- Renal and urinary disorders
Uncommon: Dehydration (caused by diarrhea or reduced fluid intake)
Rare: Renal impairment, Renal failure (due to dehydration especially in elderly with pre-existing renal disorders)
- General disorders and administration site conditions
Uncommon: Feeling unwell, Unspecific pain and sweating
Rare: Edema.

CONTRAINDICATIONS
Moxifloxacin is contraindicated in patients:
- With hypersensitivity to moxifloxacin or other quinolones and any components of this medication.
- Less than 18 years of age.
- Pregnancy and lactation.
- With history of tendon disease/disorder related to quinolone treatment.
- With impaired liver function and in patients with transaminases > 5 fold ULN.
- With congenital or documented acquired QT prolongation.
- With electrolyte disturbances, particularly in uncorrected hypokalaemia.
- With clinically relevant bradycardia.
- With clinically relevant heart failure with reduced left ventricular ejection fraction.
- With previous history of symptomatic arrhythmias.

WARNING

Fluoroquinolones, including moxifloxacin are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

PRECAUTIONS
- As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke)
- Antibiotic associated colitis have been reported with the use of broad-spectrum antibiotics including Moxifloxacin; therefore it is important to consider this diagnosis in patients who develop serious diarrhea is association with the use of Moxifloxacin
- Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients, 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 sensitive to drug associated effects on the QT interval.
- Moxifloxacin should be used with caution in patients treated concomitantly with drugs that prolong QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants, in the patients with ongoing proarrythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia, in the patients with liver cirrhosis as preexisting QT prolongation, in women and elderly patients who are susceptible to QTc prolonging drugs.
- Tendon inflammation and/or rupture have been reported with quinolone antibiotics. Risk may be increased with concurrent corticosteroids, particularly in the elderly. Discontinue at first signs or symptoms of tendon pain.
- For patients with pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), treatment with Moxifloxacin 400mg film-coated tablets is not recommended.
- Use with caution in diabetes as glucose regulation may be altered.
- Moxifloxacin is not recommended for the treatment of MRSA infections, In case of a suspected or confirmed infection due MRSA, treatment with an appropriate antibacterial agent should be started.
- 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.
- Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. If an allergic reaction occurs discontinue drug immediately.
- Quinolones should be used with caution as they may exacerbate myasthenia gravis
- Peripheral neuropathy may rarely occur.
- 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.
- Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.
- If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
- 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.

OVERDOSE AND TREATMENT
No specific counter measures 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.

DRUG INTERACTIONS
- **Antacids, Minerals, and multivitamins**
  Concomitant ingestion of Moxifloxacin together antacids, minerals and multivitamins may result in impaired absorption of moxifloxacin after oral administration due to formation of chelate complexes with the multi-valent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral drugs (e.g. didanosine), and other preparations containing magnesium or aluminum, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin dose.
- Moxifloxacin increases Cmax of digoxin by approximately 30 % at steady state without affecting AUC or trough levels.
- Concomitant administration of charcoal with an oral dose of 400mg moxifloxacin leads to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases).
- The prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.
- Concomitant administration of NSAIDs with quinolones may increase the risks of CNS stimulation and convulsions.

AVAILABILITY
Moxifloxacin (Xiflox) 400mg film coated Tablet in Alu/ Alu Blister Pack x 5's (Box of 5's).

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

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 at www.fda.gov.ph.
The patient is advised to seek immediate medical attention at the first sign of adverse drug reaction.

REGISTRATION NUMBER: DR-XY48624

DATE OF FIRST AUTHORIZATION: 14-February-2023

DATE OF REVISION: 08-May-2023

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

Getz pharma (PVT) LIMITED
www.getzpharma.com
A member of The Getz Group, USA.

PHP-200017173

Manufactured by: Getz Pharma (Pvt.) Ltd., 29-30 Sector 27, Korangi Industrial Area, Karachi - 74900, Pakistan.
Imported by: Getz Pharma (Phils.) Inc., 2/F Tower 1, The Rockwell Business Center, Ortigas Ave., Pasig City, Philippines.

210 mm

130 mm