140mm

M-Floxsel Tablet/Infusion

(M o x i f l o x a c i n)

ایم۔فلوکسیل ٹیبلیٹ/انفیوژن

(موکسی فلوکساسین)

210mm

COMPOSITION

M-Floxsel Tablet 400mg

Each film coated tablet contains:

Moxifloxacin (as HCl).....400mg

(USP Specifications)

M-Floxsel Infusion 400mg/250ml

Each 250ml contains:

Moxifloxacin (as hydrochloride).....400mg

(Innovator's Specifications)

DESCRIPTION

Moxifloxacin is a synthetic, broad-spectrum fluoroquinolone antibiotic agent that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication.

INDICATIONS

Moxifloxacin tablets are indicated for the treatment of the following bacterial infections:

- Acute exacerbation of chronic bronchitis
- Community acquired pneumonia.
- Acute bacterial sinusitis (adequately diagnosed)
- Complicated skin and skin structure infections (cSSSI)
- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess. Moxifloxacin tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae unless moxifloxacin-resistant Neisseria gonorrhoeae can be excluded.

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.

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.

DOSAGE & ADMINISTRATION

FOR TABLET:

Adults

One 400 mg film-coated tablet once daily.

Duration of administration

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

- ***Acute exacerbation of chronic bronchitis:*** 5 - 10 days
- ***Community acquired pneumonia:*** 10 days
- ***Acute sinusitis:*** 7 days
- ***Mild to moderate pelvic inflammatory disease:*** 14 days

The recommended dose (400 mg once daily) and duration of therapy for the indication being treated should not be exceeded.

FOR IV INFUSION:

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.

Children and adolescents

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.

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 - 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 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.

After a single 400 mg intravenous 1 hour infusion peak plasma concentrations of approximately 4.1 mg/l were observed at the end of the infusion corresponding to a mean increase of approximately 26% relative to those seen after oral administration (3.1 mg/l). The AUC value of approximately 39 mg·h/l after i.v. administration is only slightly higher than that observed after oral administration (35 mg·h/l) in accordance with the absolute bioavailability of approximately 91%. In patients, there is no need for age or gender related dose adjustment on intravenous moxifloxacin. Pharmacokinetics are linear in the range of 50 - 1200 mg single oral dose, up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

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.

Maximum concentrations of 5.4 mg/kg and 20.7 mg/l (geometric mean) were reached in bronchial mucosa and epithelial lining fluid, respectively, 2.2 h after an oral dose. The corresponding peak concentration in alveolar macrophages amounted to 56.7 mg/kg. In skin blister fluid concentrations of 1.75 mg/l were observed 10 h after intravenous administration. In the interstitial fluid unbound concentration time profiles similar to those in plasma were found with unbound peak concentrations of 1.0 mg/l (geometric mean) reached approximately 1.8 h after an intravenous dose.

Metabolism

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal (approximately 40%) and biliary/faecal (approximately 60%) 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.

Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose (unchanged drug and metabolites) totaled to approximately 98% after intravenous administration of the drug. 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.

WARNINGS AND PRECAUTIONS

•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 these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

•Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline. Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin.

•Therefore, the recommended dose should not be exceeded. 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. If signs of cardiac arrhythmia occur during treatment with moxifloxacin, treatment should be stopped and an ECG should be performed.

•Cases of fulminant hepatitis potentially leading to life-threatening liver failure 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.

•Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders which may predispose to seizures or lower the seizure threshold.

•Antibiotic associated colitis (incl. pseudomembranous colitis) has been reported in association with the use of broad spectrum antibiotics including moxifloxacin; therefore it is important to consider this diagnosis in patients who develop serious diarrhea during or after the use of moxifloxacin. In this situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

•Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin and rest the affected limb(s).

•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.

•If vision becomes impaired or any effects on the eyes are experienced, an eye specialist

should be consulted immediately.
•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 a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.
•Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
•For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with moxifloxacin is not recommended.
•Pelvic inflammatory disease may be caused by fluoroquinolone resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.
•Due to adverse effects on the cartilage in juvenile animals, the use of moxifloxacin in children and adolescents < 18 years is contraindicated.
•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 ischemia) 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 medication 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.
• 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.
•Moxifloxacin therapy may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth causing false negative results.
•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

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, breast-feeding is contraindicated during moxifloxacin therapy.

SIDE EFFECTS

Infections and infestations

Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis.

Blood and lymphatic system disorders

Anemia, leucopenia(s), neutropenia, thrombocytopenia, thrombocythemia, blood eosinophilia, prothrombin time prolonged/INR increased or decreased.

Immune system disorders

Anaphylaxis including very rarely life-threatening shock, allergic edema / angioedema.

Metabolism and nutrition disorders

Hyperglycemia, hyperuricemia, hyperlipidemia, hypoglycemia.

Psychiatric disorders

Anxiety reactions, psychomotor hyperactivity/ agitation, emotional lability, depression (in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideations/ thoughts, or suicide attempts), hallucination, depersonalization, psychotic reactions.

Nervous system disorders

Headache, dizziness, par- and dysaesthesia, taste disorders (incl. ageusia in very rare cases),
confusion and disorientation, sleep disorders (predominantly insomnia), tremor, vertigo, somnolence, hypoaesthesia, smell disorders (incl. anosmia), abnormal dreams, disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo)

Cardiac disorders

QT prolongation, palpitations, tachycardia, atrial fibrillation, angina pectoris, ventricular tachyarrhythmias, syncope (i.e., acute and short lasting loss of consciousness).

Respiratory, thoracic and mediastinal disorders

Dyspnea (including asthmatic conditions).

Gastrointestinal disorders

Decreased appetite and food intake, constipation, dyspepsia, flatulence, gastritis, increased amylase, dysphagia, stomatitis, antibiotic associated colitis, nausea, vomiting, gastrointestinal and abdominal pains, diarrhoea.

Hepatobiliary disorders

Hepatic impairment (incl. LDH increase), increased bilirubin, increased gamma-glutamyl-transferase, increase in blood alkaline phosphatase, fulminant hepatitis potentially leading to life-threatening liver failure.

Musculoskeletal and connective tissue disorders

Tendonitis, Muscle cramp, Muscle twitching, Muscle weakness, Tendon rupture, Arthritis, Muscle rigidity, Exacerbation of symptoms of myasthenia gravis, Arthralgia, Myalgia.

Renal and urinary disorders

Renal impairment (incl. increase in BUN and creatinine), renal failure, dehydration.

DRUG INTERACTIONS

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 antidepressive agents
•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, sucralfate and agents containing iron or zinc) and administration of moxifloxacin.
•Concomitant administration of charcoal with an oral dose of 400 mg moxifloxacin led to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended.
•After repeated dosing in healthy volunteers, moxifloxacin increased Cmax 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 hyperglycaemia. However, the observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

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 hypokalaemia.
•Clinically relevant bradycardia.
•Clinically relevant heart failure with reduced left-ventricular ejection fraction.
•Previous history of symptomatic arrhythmias.
•Moxifloxacin should not be used concurrently with other drugs that prolong the QT interval.
Due to limited clinical data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5 fold ULN.

STORAGE & INSTRUCTIONS

Store between 15-25°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

M-Floxsel Tablet 400mg
1x5's, 10x10's tablets.
M-Floxsel Infusion 400mg/250ml
250ml vial.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی، نمی سے محفوظ اور بچوں کی پہنچ سے دور رکھیں صرف ایک بار استعمال کے لیے۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
PHARMASOL PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.