Mob
(Moxifloxacin)

COMPOSITION

Mob Tablets 400mg

Each film coated tablet contains:
Moxifloxacin.....400mg
(As Moxifloxacin Hydrochloride BP).
Finished Product Specs.: BP.

Mob IV Infusion 400mg/250ml

Each 250ml contains:
Moxifloxacin 400mg
(As Moxifloxacin Hydrochloride BP).
Finished Product Specs.: In-house.

DESCRIPTION

Mob (Moxifloxacin) is an oral 8-methoxyfluoroquinolone antibacterial agent. Chemically, Moxifloxacin is a monohydrochloride salt of 1-cyclopropyl-7-[(S, S)-2, 8-diazabicyclo [4.3.0] non-8- yl]-6-fluoro-8-methoxy-1, 4-dihydro-4-oxo-3 quinoline carboxylic acid. The molecular formula is $C_{21}H_{25}ClFN_3O_4$.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of action: 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. 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.

Microbiological Susceptibility:

Aerobic gram-positive micro-organisms: Gardnerella vaginalis, Staphylococcus aureus (methicillin-susceptible), Streptococcus agalactiae (Group B), 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). Aerobic gram-negative micro-organisms: Acinetobacter baumanii, Haemophilus influenza, Haemophilus parainfluenzae, Legionella pneumophila, Moraxella (Branhamella) catarrhalis.

Anaerobic micro-organisms: Prevotella spp., Prevotella spp.

Other micro-organisms: Chlamydophila (Chlamydia) pneumoniae, Chlamydia trachomatis, Coxiella burnetii, Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma hominis, Mycoplasma pneumoniae.

Pharmacokinetics

Absorption:

Tablets: Following oral administration, moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91%. Pharmacokinetics are linear in the range of 50-800mg single dose and up to 600mg once daily dosing over 10 days. Following a 400mg oral dose peak concentrations of 3.1mg/L are reached within 0.5-4 h post administration.

Infusion: After a single 400mg intravenous 1 hour infusion peak plasma concentrations of approximately 4.1mg/L were observed at the end of the infusion corresponding to a mean increase of approximately 26% relative to those seen after oral administration (3.1mg/L). The AUC value of approximately 39mg.h/L after IV administration is only slightly higher than that observed after oral administration (35mg.h/L) in accordance with the absolute bioavailability of approximately 91%.

Distribution:

Tablets and Infusion: Moxifloxacin is distributed to extravascular spaces rapidly. The steady-state volume of distribution (Vss) is approximately 2L/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.

Metabolism:

Tablets and Infusion: 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:

Tablets and Infusion: 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 drug from the kidneys.

Special Population:

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 >20ml/min/1.73m^2).

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.

THERAPEUTIC INDICATIONS

Mob (Moxifloxacin) is indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin. In the following indications, Moxifloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections:

- Acute bacterial sinusitis.
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis.

In the following indications, 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 or when these have failed:

- Community acquired pneumonia, except severe cases.
- 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.

Mob (Moxifloxacin) is 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.

Mob (Moxifloxacin) may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:

- Community-acquired pneumonia.
- Complicated skin and skin structure infections.

Mob (Moxifloxacin) should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

DOSAGE AND ADMINISTRATION

Tablets:

Dose: The recommended dose is one 400mg film coated tablet once daily.
Method of administration: The film coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.
Duration of administration: Moxifloxacin 400mg film coated tablets should be used for the following treatment durations:

- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis: 5-10 days.
- Community acquired pneumonia: 10 days.
- Acute bacterial sinusitis: 7 days.
- Mild to moderate pelvic inflammatory disease: 14 days.

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

Infusion:

Dose: The recommended dose is 400mg moxifloxacin, infused once daily. Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400mg tablets, when clinically indicated.

Method of administration: It should be administered through constant infusion over 60 minutes. If medically indicated, the solution for infusion can be administered via a T-tube, together with a compatible infusion solution.

Duration of administration: In clinical studies most patients switched to oral therapy within 4 days (in community acquired pneumonia i.e. CAP) or 6 days (in complicated skin and skin structure infections i.e. cSSSI). The recommended total duration of intravenous and oral treatment is 7-14 days for CAP and 7-21 days for cSSSI.

Special Population:

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. haemodialysis and continuous ambulatory peritoneal dialysis.
Elderly and patients with low bodyweight: No adjustment of dosage is required in these populations.

Paediatric population: Moxifloxacin is contraindicated in children and adolescents (<18 years of age). Efficacy and safety of moxifloxacin in children and adolescents has not been established.

CONTRAINDICATIONS

- Hypersensitivity to moxifloxacin, other quinolones or to any of its 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.

ADVERSE REACTIONS

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

Blood and lymphatic system disorders: Anaemia, leucopenia, neutropenia, thrombocytopenia, thrombocythemia, blood eosinophilia and prolonged prothrombin time / increased INR.

Immune system disorders: Allergic reaction.

Metabolism and nutrition disorders: Hyperlipidemia, hyperglycemia and hyperuricemia.

Psychiatric disorders:* Anxiety reactions and psychomotor hyperactivity/ agitation.

Nervous system disorders:* Headache, dizziness, taste disorders, confusion and disorientation, sleep disorders, tremor, vertigo and somnolence.

Eye disorders:* Visual disturbances including diplopia and blurred vision especially in the course of CNS reactions.

Ear and labyrinth disorders:* Tinnitus and hearing impairment including deafness (usually reversible).

Cardiac disorders: QT prolongation in patients with hypokalaemia, palpitations, tachycardia, atrial fibrillation and angina pectoris.

Vascular disorders: Vasodilatation, hypertension, hypotension and vasculitis.

Respiratory, thoracic and mediastinal disorders: Dyspnea (including asthmatic conditions).

Gastrointestinal disorders: Nausea, vomiting, gastrointestinal and abdominal pains, diarrhea, decreased appetite and food intake, constipation, dyspepsia, flatulence, gastritis and increased amylase.

Hepatobiliary disorders: Increase in transaminases, hepatic impairment (including increased LDH), increased bilirubin, increased gamma-glutamyl-transferase, increase in blood alkaline phosphatase, jaundice and hepatitis (predominantly cholestatic).

Skin and subcutaneous tissue disorders: Pruritus, rash, urticaria and dry skin.

Musculoskeletal and connective tissue disorders:* Arthralgia and myalgia.

Renal and urinary disorders: Dehydration.

General disorders and administration site conditions:* Infusion site reactions, feeling unwell (predominantly asthenia or fatigue), painful conditions (including pain in back, chest, pelvic and extremities), sweating, infusion site thrombophlebitis.

* 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.

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 anaemia, rhabdomyolysis, photosensitivity reactions.

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 such medicinal product is contraindicated.
- 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 high dose enemas, 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 400mg 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.
- 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.
- A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

WARNINGS AND PRECAUTIONS

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.

Prolongation of QTc interval: Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. Medications that can reduce potassium levels should be used with caution in patients receiving moxifloxacin. Hypersensitivity/allergic reactions: In cases of clinical manifestations of severe hypersensitivity reactions moxifloxacin should be discontinued and suitable treatment should be initiated.

Severe liver disorders: Liver failures (including fatal cases) have been reported with moxifloxacin. Patients should contact their doctor prior to continuing treatment if signs and symptoms such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy is observed.

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, hypoaesthesia, dysaesthesia, 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 potentially irreversible condition.

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.

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

Lactation: 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.

Additional Precautions for Infusion: Moxifloxacin 400mg infusion is compatible with these co-infusions: Water for injection, Sodium chloride 0.9%, Sodium chloride 1 molar, Glucose 5%,10% & 40%, Xylitol 20%, Ringer's solution, Compound Sodium Lactate Solution (Hartmann's Solution, Ringer-Lactate Solution). Moxifloxacin infusion should not be co-infused with other drugs.

Do not use the infusion if there is any visible particulate matter or if the solution is cloudy. At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution below 15°C.

This product is for single use only. Any unused solution should be discarded.

OVERDOSAGE:

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 400mg oral or intravenous moxifloxacin will reduce systemic availability of the drug by more than 80% or 20% respectively. 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.

STORAGE CONDITIONS

Tablets:
- Store below 30°C.
- Protect from heat, light and moisture.

Infusion:
- Store below 30°C.
- Protect from heat and light.

PRESENTATION

Mob Tablets 400mg: Available as pack of 5 film coated tablets.

Mob IV Infusion 400mg/250ml: Available in glass vial of 1's.

To be sold on the prescription of a registered medical practitioner only.

Keep all medicines out of the reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
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