PROFESSIONAL INFORMATION FOR

MOFLOXX TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

MOFLOXX (Tablets)

COMPOSITION:

Each film-coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

Inactive ingredients are corn starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry pink (containing hypromellose, red iron oxide, macrogol and titanium dioxide), and povidone.

Contains 93,6 mg lactose monohydrate per tablet.

PHARMACOLOGICAL CLASSIFICATION:

A. 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Moxifloxacin is a fluoroquinolone antibiotic with a broad spectrum of bactericidal action.

Microbiology:

Moxifloxacin is active against a wide range of aerobic Gram-positive and Gram-negative organisms. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination. It appears that the C-8 methoxy moiety contributes to the enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines. Therefore, micro-organisms resistant to these classes of antibiotics may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Species for which acquired resistance may be a problem:

Aerobic Gram-positive micro-organisms:

Enterococcus faecalis[*]

Enterococcus faecium[*]

Staphylococcus aureus (methicillin-resistant) [+]

Aerobic Gram-negative micro-organisms:

Enterobacter cloacae[*]

Escherichia coli[*]

Klebsiella pneumoniae[*#]

Klebsiella oxytoca

Neisseria gonorrhoeae[*+]

Proteus mirabilis[*]

Anaerobic micro-organisms:

Bacteroides fragilis[*]

Peptostreptococcus spp.[*]

Inherently resistant organisms:

Aerobic Gram-negative micro-organisms:

Pseudomonas aeruginosa

[*]Activity has been satisfactorily demonstrated in susceptible strains in studies in the approved indications.

[#]ESBL-producing strains are commonly resistant to fluoroquinolones, such as moxifloxacin.

[+]Resistance rate > 50 % in one or more countries.

<u>Pharmacokinetic properties:</u>

Following oral administration moxifloxacin is well absorbed. The absolute bioavailability amounts to approximately 90 % after oral administration of a 400 mg dose.

Pharmacokinetics are linear in the range of 50 – 1200 mg single oral doses and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 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.

Food does not impair oral absorption but may delay the time to peak serum concentrations.

Moxifloxacin is distributed to extravascular spaces. Exposure to moxifloxacin in terms of AUC (AUC_{norm} = 6 kg*h/ℓ) is high; the volume of distribution at steady state amounts to Vss of approximately 2 ℓ/kg. In saliva, peak concentrations similar to those in plasma may be reached. Due to low protein binding (approximately 45 %), high free peak concentrations > 10 x MIC are observed. Moxifloxacin is mainly bound to serum albumin.

In tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polyps) and inflamed lesions (cantharide blister fluid), concentrations exceeding those in the plasma are reached.

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary / faecal pathways as unchanged compound 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. The recovery from urine (approximately 19 % for unchanged compound, 2,5 % for M1, and approximately 14 % for M2) and faeces (approximately 25 % of unchanged compound, 36 % for M1 and no recovery for M2) totals to approximately 96,98 % of the dose.

Moxifloxacin is eliminated from plasma and saliva 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 amounts to about 24 – 53 mℓ/min, suggesting partial tubular reabsorption of the medicine from the kidneys. Approximately 19 % of the dose is excreted unchanged into the urine and approximately 25 % in the faeces. Approximately 2,5 % is recovered as M1 in the urine and 36 % in the faeces, respectively. About 14 % is recovered as M2 in the urine.

INDICATIONS:

MOFLOXX is indicated for the treatment of severe and/or complicated infections caused by moxifloxacin sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

MOFLOXX is not indicated/approved for the initiation of treatment (first line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to moxifloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

MOFLOXX is indicated for the treatment of adults (> 18 years of age) with mild to moderately severe infections of the designated micro-organisms, where these indications are compliant with the indication context listed below:

- Acute bacterial sinusitis caused by *Haemophilus influenzae*, or *Moraxella catarrhalis*.
- Acute exacerbations of chronic obstructive pulmonary disease (COPD) including chronic bronchitis (AECB) caused by *Haemophilus influenza*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.
- Community acquired pneumonia (of mild to moderate severity) caused by *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Moraxella catarrhalis*.
- Severe and/or complicated skin and skin structure infections (including diabetic foot infections) caused by *Staphylococcus aureus, Streptococcus. Pyogenes, Enterococcus faecalis, Escherichia coli, Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis, or Enterobacter cloacae.*
- Uncomplicated pelvic inflammatory disease not caused by *Neisseria gonorrhoea* (i.e. infections of female upper genital tract, including salpingitis and endometritis).

- Severe and/or complicated intra-abdominal infections including polymicrobial infections such as abscesses.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to **MOFLOXX**. Therapy with **MOFLOXX** may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

CONTRAINDICATIONS:

MOFLOXX is contraindicated in:

- Patients with known hypersensitivity to moxifloxacin, any component of the tablets or any of the other quinolone compounds.
- Children under the age of 18 years and in growing adolescents.
- Pregnancy and lactation (see **"HUMAN REPRODUCTION"**). Quinolones are known to distribute well into breast milk of lactating women. The use of **MOFLOXX** in pregnancy and nursing mothers is contraindicated.
- Patients with a history of tendon, muscle, joint nerve, central nervous system or psychiatric disorders especially those related to previous quinolone/fluoroquinolone use where alternative appropriate antibiotic choices are available.

- Congenital or documented acquired QT prolongation (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Electrolyte disturbances, particularly uncorrected hypokalaemia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Clinically relevant bradycardia.
- Clinically relevant heart failure with reduced left-ventricular ejection fraction.
- Patients with a previous history of symptomatic dysrhythmias.
- Patients who are concurrently using other medicines that prolong the QT interval (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).
- Patients with impaired liver function (Child-Pugh C) and in patients with transaminases increase > 5-fold upper limit of normal (ULN) due to limited clinical data (see **"DOSAGE AND DIRECTIONS FOR USE"**).
- Concomitant use of **MOFLOXX** with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment and the elderly.
- history of convulsions, epilepsy or difficult to control epilepsy disorders.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection where alternative antibiotic choices are available.
- Use of **MOFLOXX** is contraindicated in patients with confirmed mitral valve and aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.

MOFLOXX is contraindicated in children under 18 years and in growing adolescents (except where no other suitable antimicrobial agent can be used). Experimental evidence indicates that species variable reversible lesions of the cartilage of weight bearing joints have been seen in immature members of certain animal species.

WARNINGS AND SPECIAL PRECAUTIONS:

THE SAFETY AND EFFICACY OF MOFLOXX IN PAEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED (see **"CONTRAINDICATIONS" and "HUMAN REPRODUCTION").**

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions:

MOFLOXX HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. IT SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALAEMIA AND PATIENTS RECEIVING CLASS 1A (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTI-DYSRHYTHMIC AGENTS, DUE TO THE LACK OF CLINICAL EXPERIENCE WITH MOFLOXX IN THESE PATIENT POPULATIONS.

Patients should be advised that **MOFLOXX** may produce changes in the electrocardiogram (QTc interval prolongation) (see **"CONTRAINDICATIONS"**). Treatment with **MOFLOXX** should be stopped if signs or symptoms that may be associated with cardiac dysrhythmia occur during treatment, with or without ECG findings.

Pharmacokinetic studies between moxifloxacin, as in **MOFLOXX**, and other medicines that prolong the QT interval, such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of **MOFLOXX** and these medicines cannot be excluded; therefore, **MOFLOXX** should not be given concurrently with these medicines (see **"CONTRAINDICATIONS"**).

MOFLOXX should be used with caution in patients who are taking medicines that can reduce potassium levels (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).

MOFLOXX should be used with caution in patients who are taking medicines associated with clinically significant bradycardia (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**). Patients should be advised to inform their medical practitioner of any other medicines when taken concurrently with **MOFLOXX**, including over-the-counter medicines.

The effect of **MOFLOXX** on patients with congenital prolongation of the QT interval has not been studied; however, it is expected that these individuals may be more susceptible to medicine-induced QT prolongation. Because of limited clinical experience, **MOFLOXX** should not be used in patients with ongoing pro-dysrhythmic conditions, such as recent

hypokalaemia, clinically significant bradycardia and acute myocardial ischaemia (see **"CONTRAINDICATIONS"**). Patients should be advised to inform their medical practitioner of any personal or family history of QTc prolongation or pro-dysrhythmic conditions.

The magnitude of QT prolongation may increase with increasing concentrations of **MOFLOXX**; therefore, the recommended dose should not be exceeded.

QT prolongation may lead to an increased risk of ventricular arrhythmias, including torsade de pointes. In patients with paired valid ECG's in phase III clinical trials, the mean ± SD (standard deviation) effect of moxifloxacin, as in **MOFLOXX**, 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin, as in **MOFLOXX**, treatment in over 4000 patients; however, certain predisposing conditions may increase the risk for ventricular dysrhythmias.

MOFLOXX should be used with caution in patients with any condition predisposing to cardiac dysrhythmias (e.g. acute myocardial ischaemia) because they may have an increased risk of developing ventricular dysrhythmias (including torsade de pointes) and cardiac arrest (see **"CONTRAINDICATIONS"** and **"INTERACTIONS"**).

Female patients and elderly patients may be more sensitive to the effects of QTc prolonging medicines, such as **MOFLOXX**, and therefore special caution is required.

Patients should be advised to contact their medical practitioner if they experience palpitations or fainting spells while taking **MOFLOXX**.

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis) (see **"CONTRAINDICATIONS"**).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

Paediatric patients:

The oral administration of moxifloxacin, as in **MOFLOXX**, causes lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class medicines also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature

animals of various species (see **“CONTRAINDICATIONS”** and **"HUMAN REPRODUCTION"**).

Patients predisposed to seizures:

Convulsions have been reported in patients receiving quinolones. Quinolones, including **MOFLOXX**, may also cause central nervous system (CNS) events, including dizziness, confusion, tremors, hallucinations, depression, anxiety, insomnia, nightmares or paranoia, agitation, nervousness and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving **MOFLOXX**, **MOFLOXX** should be discontinued and appropriate measures instituted. **MOFLOXX** should be used with caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (see **"SIDE EFFECTS"**).

Hypersensitivity / allergic reactions:

Serious and occasionally fatal hypersensitivity (anaphylactic) and allergic reactions, some following the first dose, have been reported in patients receiving fluoroquinolone, including **MOFLOXX**, therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine (adrenaline). **MOFLOXX** should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous

steroids, and airway management, including intubation, may be administered as indicated (see **"SIDE EFFECTS"**).

Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain aetiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice and hepatic necrosis.

Antibiotic-associated diarrhoea, including colitis:

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported with MOFLOXX, and may range in severity from mild to life-threatening colitis. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of MOFLOXX.

Treatment with antibacterial agents, such as **MOFLOXX**, alters the normal flora of the colon and may permit overgrowth of clostridia. Ongoing treatment with antibacterial agents, including **MOFLOXX**, should be discontinued and therapeutic measures should be initiated if AAD or AAC is suspected or after the diagnosis has been established. Mild cases of pseudomembranous colitis usually respond to **MOFLOXX** discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent

clinically effective against *Clostridium difficile* colitis to reduce the risk of transmission. Medicines that inhibit peristalsis are contraindicated in patients who develop serious diarrhoea.

Tendon inflammation, tendon rupture:

Achilles and other tendon inflammation and rupture, sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with quinolones, including **MOFLOXX**. These ruptures occurred within 2 to 42 days after the start of therapy. Age and concomitant use of corticosteroids with **MOFLOXX** may increase the risk of tendon disorders or ruptures. **MOFLOXX** should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon and the patient should refrain from exercise until the diagnosis has been confirmed. A healthcare professional should be consulted immediately and will initiate appropriate treatment (e.g. immobilisation) of the affected tendon.

Peripheral neuropathy:

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones, including **MOFLOXX**. Patients under treatment with **MOFLOXX** should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see **"SIDE EFFECTS"**). **MOFLOXX** should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Patients with myasthenia gravis:

MOFLOXX should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Severe liver disorders:

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with **MOFLOXX** (see **"SIDE-EFFECTS"**). 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 (see **"CONTRAINDICATIONS"**).

Serious bullous skin reactions:

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with **MOFLOXX** (see **"SIDE EFFECTS"**). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Psychiatric reactions:

Psychiatric reactions may occur even after the first administration of quinolones, including **MOFLOXX**. In some cases, depression or psychotic reactions have progressed to

suicidal thoughts and self-injurious behaviour, such as suicide attempts (see **"SIDE-EFFECTS"**). In the event that the patient develops these reactions, **MOFLOXX** should be discontinued and appropriate measures instituted. Caution is recommended if **MOFLOXX** is to be used in psychotic patients or in patients with history of psychiatric disease.

Patients with renal impairment:

Elderly patients with renal disorders should use **MOFLOXX** with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

Concomitant use of **MOFLOXX** and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment and the elderly (See **"CONTRAINDICATIONS"**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/angiotensin receptor blockers.

Patients should be advised that **MOFLOXX** tablets may be taken with or without meals, and to drink fluids liberally.

Cardiac disorders:

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough

cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see **"CONTRAINDICATION"**).

Vision disorders:

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **"SIDE EFFECTS"**).

Prevention of photosensitivity reactions:

Patients should be advised that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with **MOFLOXX** at the recommended dose. In keeping with good medical practice, patients should avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If sunburn-like reaction or skin eruptions occur, patients should contact their medical practitioner.

Patients with glucose-6-phosphate dehydrogenase deficiency:

Patients with a family history of or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, **MOFLOXX** should be used with caution in these patients.

Patients with special complicated skin and skin structure infections:

Clinical efficacy of **MOFLOXX** in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Interference with biological tests:

MOFLOXX therapy may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving **MOFLOXX**.

Patients with MRSA infections:

MOFLOXX 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 (see **"Pharmacodynamic properties"**).

Lactose:

MOFLOXX contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **MOFLOXX**.

Effects on ability to drive and use machines:

MOFLOXX may cause dizziness and light-headedness; therefore, patients should know how they react to **MOFLOXX** before they operate a vehicle or machinery or engage in activities requiring mental alertness or coordination.

INTERACTIONS:

Medicines that may prolong the QT interval:

An additive effect on QT interval prolongation of **MOFLOXX** and other medicines that may prolong the QTc interval cannot be excluded. This may lead to an increased risk of ventricular dysrhythmias, including torsade de pointes. Therefore, co-administration of **MOFLOXX** with any of the following medicines is contraindicated (see **"CONTRAINDICATIONS"**):

- Anti-dysrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide).
- Anti-dysrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride).
- Tricyclic antidepressants (e.g. amitriptyline, trimipramine, desimipramine).
- Certain antimicrobial medicines (saquinavir, sparfloxacin, erythromycin, pentamidine, antimalarials particularly halofantrine).
- Certain antihistaminics (astemizole, mizolastine).
- Others (cisapride, vincamine IV, bepridil, diphemanil).

MOFLOXX should be used with caution in patients who are taking medicine that can reduce potassium levels [e.g. loop and thiazide-type diuretics, laxatives and enemas (high doses), corticosteroids, amphotericin B] or medicine that is associated with clinically significant bradycardia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Food and dairy products:

Absorption of **MOFLOXX** is not altered by food intake. Therefore, **MOFLOXX** can be administered independent from food intake.

Ranitidine:

Concomitant administration with ranitidine does not change the absorption characteristics of **MOFLOXX** significantly. Absorption parameters (C_{max}, t_{max}, AUC) are similar, indicating absence of an influence of gastric pH on **MOFLOXX** uptake from the gastrointestinal tract.

Antacids, minerals and multivitamins:

Concomitant ingestion of **MOFLOXX** with antacids, minerals and multivitamins may result in impaired absorption of **MOFLOXX** due to the formation of chelated complexes with the multivalent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, antiretroviral agents and other preparations containing magnesium, aluminium and other minerals, such as iron, should be administered at least 4 hours before or 2 hours after ingestion of **MOFLOXX**.

Warfarin:

Increased anticoagulant activity may occur in patients receiving oral anticoagulants concurrently with **MOFLOXX**. Infectious and inflammatory conditions, advanced age and poor general status of the patient are risk factors. International Normalised Ratio (INR)

monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Digoxin:

The pharmacokinetics of digoxin are not significantly influenced by **MOFLOXX** (and vice versa).

Itraconazole:

The pharmacokinetics of **MOFLOXX** are not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with **MOFLOXX** and vice versa.

Theophylline:

No influence of **MOFLOXX** on theophylline pharmacokinetics (and vice versa) at steady state was detected. Hence, no recommendations with respect to theophylline dosing need to be given.

Probenecid:

Probenecid has no significant effect on apparent total body clearance and renal clearance of **MOFLOXX**. Therefore, dosing adjustments need not be made when both medicines are administered concurrently.

Antidiabetic agents:

Concomitant administration of **MOFLOXX** with glibenclamide may result in a decrease of approximately 21 % in the peak plasma concentrations of glibenclamide.

Oral contraceptives:

No interaction has occurred following concomitant oral administration of **MOFLOXX** with oral contraceptives.

Calcium supplements:

No interaction occurs following concomitant oral administration of **MOFLOXX** with calcium supplements.

Morphine:

Parenteral administration of morphine with **MOFLOXX** does not reduce the oral bioavailability of **MOFLOXX**.

Atenolol:

The pharmacokinetics of atenolol are not significantly altered by **MOFLOXX**. Administration of **MOFLOXX** with atenolol may result in a marginal increase of the AUC (by approximately 4 %) and a decrease in peak concentrations by 10 %.

ACE inhibitors /Angiotensin receptor blockers:

Concomitant use of **MOFLOXX** and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment and the elderly (see **"CONTRAINDICATIONS"**).

Medicines metabolised by cytochrome P450 enzymes:

MOFLOXX does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP219, or CYP1A2 *in vitro*. Therefore, **MOFLOXX** is unlikely to alter the pharmacokinetics of medicines metabolised by these enzymes (e.g. midazolam, ciclosporin, warfarin, and theophylline).

Non-steroidal anti-inflammatory medicines (NSAIDS):

The concomitant administration of a non-steroidal anti-inflammatory medicine with **MOFLOXX** may increase the risks of CNS stimulation and convulsions (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Charcoal:

Concomitant administration of charcoal with a dose of 400 mg **MOFLOXX** will reduce systemic availability of the medicine by more than 80 %.

HUMAN REPRODUCTION:

The use of **MOFLOXX** during pregnancy and lactation is not recommended as safety has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Dosage:

The recommended dose for **MOFLOXX** is 400 mg once daily for all indications. The tablets should be swallowed whole with a glass of water. **MOFLOXX** can be administered independent of food intake.

Duration of treatment:

The duration of treatment to contain and eradicate an infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. In general, antibiotic therapy should continue for 3 – 4 days after the manifestations of the infection have cleared.

The following general recommendations for the treatment of upper and lower respiratory tract infections are made:

Acute exacerbation of chronic obstructive pulmonary disease (COPD) including chronic bronchitis:	5 days
Acute sinusitis:	10 days
Community acquired pneumonia:	10 days
Uncomplicated pelvic inflammatory disease not caused by *Neisseria gonorrhoea* (i.e. infections of female upper genital tract, including salpingitis and endometritis).	14 days

The recommended duration of treatment for skin and soft tissue infections is 10 days.

Moxifloxacin, as in **MOFLOXX**, has been studied in clinical trials for up to 14 days treatment.

Special populations:

Children:

The use of **MOFLOXX** in children and adolescents in the growth phase is contraindicated.

Elderly:

No adjustment of dosage is required in the elderly.

Hepatic impairment:

No dosage adjustment is required in patients with slightly impaired liver function (Child-Pugh A). No pharmacokinetic data is available for patients with moderate to severely impaired liver function (Child-Pugh B and C). Due to lack of data, **MOFLOXX** is not recommended in patients with moderate to severe hepatic impairment (see **"CONTRAINDICATIONS"**).

Renal impairment:

No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance ≤ 30 mℓ/min / 1,73 m^2). There is no pharmacokinetic data available in patients on dialysis treatment, or in patients with advanced renal impairment who are not on a dialysis programme. **MOFLOXX** should therefore not be used in these patients.

SIDE EFFECTS:

Infections and infestations:

Less frequent:	Moniliasis, including oral and vaginal moniliasis, and *Clostridium difficile* diarrhoea (see **"Gastrointestinal disorders"**).
Frequent:	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis

Blood and lymphatic system disorders:

Less frequent: Leucopenia, decreased or increased prothrombin, eosinophilia, anaemia, thrombocythemia, thrombocytopenia, and decreased thromboplastin.

Immune system disorders:

Less frequent: Allergic reactions, anaphylactic reaction, and shock (anaphylactic; possibly life-threatening), angioedema.

Psychiatric disorders:

Less frequent: Anorexia, insomnia, anxiety, confusion, depression, hallucinations, depersonalisation, agitation, emotional lability, sleep disorders, abnormal thinking, abnormal dreams, acute psychosis.

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Nervousness, somnolence, Guillain-Barre Syndrome, tremor, paraesthesia, peripheral neuropathy and polyneuropathy, hypertonia, incoordination, amnesia, aphasia, speech disorders, hypoesthesia, convulsions,

	disturbed coordination leading to fall with injuries especially in the elderly and parosmia. Central nervous system stimulation (including acute psychosis) has been reported (see **"Psychiatric disorders"**).
Eye disorders:	
Less frequent:	Amblyopia, abnormal vision, photophobia, uveitis and bilateral acute iris transillumination
Ear and labyrinth disorders:	
Frequent:	Vertigo.
Less frequent:	Tinnitus, hearing impairment including deafness (usually reversible).
Cardiac disorders:	
Frequent:	QT prolongation in patients with concomitant hypokalaemia.
Less frequent:	Chest pain, tachycardia, palpitations, in addition, abnormal electrocardiograms, atrial fibrillation, ventricular dysrhythmias: aortic aneurysm and dissection supraventricular tachycardia, and ventricular tachycardia have been reported.
Very rare:	Torsade de Pointes and acute myocardial ischemia.

Vascular disorders:

Less frequent: Peripheral oedema, hypertension, hypotension, vasodilation, vasculitis and syncope

Respiratory, thoracic and mediastinal disorders:

Less frequent: Asthma, dyspnoea.

Gastrointestinal disorders:

Frequent: Abdominal pain, nausea, diarrhoea, vomiting.

Less frequent: Dry mouth, flatulence, constipation, stomatitis, gastrointestinal disorder, glossitis, gastritis, tongue discolouration, dysphagia, and taste loss, *Clostridium difficile*-induced pseudomembranous colitis, dyspepsia (see **"Infections and infestations"**).

Hepatobiliary disorders:

Frequent: Abnormal liver function tests.

Less frequent: GGT, bilirubin and hepatic impairment increase and jaundice. Hepatotoxicity has been reported.

Skin and subcutaneous tissue disorders:

Less frequent: Rash (maculopapular, purpuric, pustular), pruritus, sweating, and urticaria. In addition, phototoxicity, photosensitivity and Steven-Johnson syndrome have been reported.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia, arthritis, increased muscle tone and cramping and tendon disorders (including tendinitis and tendon rupture)

Renal and urinary disorders:

Less frequent: Abnormal kidney function. Haematuria, interstitial nephritis and dysuria have also been reported. Dehydration caused by diarrhoea or reduced fluid intake.

Reproductive system and breast disorders:

Less frequent: Vaginitis.

General disorders and administrative site conditions:

Frequent: Asthenia, pain, back pain, malaise, and leg pain.

Less frequent: Pelvic pain, facial oedema, sweating

Investigations:

Less frequent: Abnormal laboratory tests, increased GGT, increased amylase, hyperglycaemia, hyperlipaemia, hyperuricaemia, increased LDH (in connection with abnormal liver function tests).

The most common changes in laboratory parameters without regard to medicine relationship and which are not listed above as adverse drug reactions, include increased and decreased haematocrit, increased white blood cell counts, increased and decreased red blood cell counts, decreased blood glucose, decreased haemoglobin, increased alkaline phosphatase, increased AST, increased ALT, increased bilirubin, increased urea, increased creatinine, and increased blood urea. It is not known whether these abnormalities were caused by the medicine or the underlying condition being treated.

Post-marketing Experience:

Cases of mitral and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post marketing, information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No specific countermeasures after accidental overdosage are recommended. General supportive therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg oral **MOFLOXX** will reduce systemic availability of the medicine by more than

80 %. The application of charcoal may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of oral overdose.

IDENTIFICATION:

Pink coloured, film-coated, capsule-shaped, biconvex tablets, plain on both sides.

PRESENTATION:

Supplied in PVC/PE/PVDC film, plain aluminium foil blister strips of 5 and 10 tablets packed in a carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C, in a dry place, protected from light and moisture.

Keep blisters in the carton, until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

44/20.1.1/1063

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

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