Flonoxin 400mg tablet

DESCRIPTION:
Flonoxin 400mg tablet: Dull red, 17 mm oblong shaped, plain on both sides, film-coated tablet.

COMPOSITION:
Each film coated tablet contains Moxifloxacin Hydrochloride equivalent to 400 mg Moxifloxacin

PHARMACODYNAMICS:
Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones
ATC Code: J01MA14

Mechanism of action
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 eg. *Mycoplasma spp., Chlamydia spp.* and *Legionella spp.*.

Moxifloxacin is effective against ß-lactam and macrolide resistant bacteria. Studies in animal models of infection have demonstrated the high in vivo activity.

PHARMACOKINETICS:
Absorption and bioavailability:
Following oral administration moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability amounts to approx. 91%.

Pharmacokinetics are linear in the range of 50 - 1200 mg single dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5 - 4 hours post application. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of fluoroquinolones, this effect is clinically not relevant. Therefore, Flonoxin can be administered independently from meals.

Distribution:
Moxifloxacin is distributed very rapidly to extravascular spaces. Exposure to drug in terms of AUC (AUCnorm = 6 kg*h/l) is high with a volume of distribution at steady state (Vss) of approximately 2 L/kg. In saliva peak concentrations higher than those of plasma may be reached. In in vitro and ex-vivo experiments over a range of 0.02 to 2 mg/l a protein binding of approximately 45 % independent from the concentration of the drug was determined. Moxifloxacin is mainly bound to serum albumin. Due to this low value high free peak concentrations > 10 x MIC are observed.

Moxifloxacin reaches high concentrations in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide 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.

Metabolism:
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. Neither in in vitro nor in clinical Phase I studies metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving Cytochrome P-450 enzymes were observed.

Independent from the route of administration the metabolites M1 and M2 are found in the plasma at concentrations lower than the parent drug. Preclinical investigations adequately covered both metabolites thus excluding potential implications with respect to safety and tolerability.

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 ranitidine and probenecid did not alter renal clearance of the drug.

PRECLINICAL SAFETY DATA
In a local tolerability study performed in dogs, no signs of local intolerability were seen when moxifloxacin was administered intravenously. After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

Carcinogenicity, Mutagenicity:
Moxifloxacin, like other fluoroquinolones, was genotoxic in vitro tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and -at higher concentrations- by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In in-vivo tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

ECG:
At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT-interval. Toxicological studies performed in dogs using oral doses of > 90 mg/kg leading to plasma concentrations > 16 mg/l caused QT-prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50 fold the human dose (> 300 mg/kg), leading to plasma concentrations of > 200 mg/l (more than 30 fold the therapeutic level after intravenous administration), reversible, non-fatal ventricular arrhythmias were seen.

Arthrotoxicity:
Fluoroquinolones are known to cause lesions in the cartilage of the major diarthodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times maximum recommended therapeutic dose (400 mg/50 kg person) on a mg/kg basis, with plasma concentrations two to three times higher than those at the recommended therapeutic dose.

Reprotoxicity:
Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (per os and i.v.) and monkeys (per os) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. Skeletal malformations were observed in rabbits that had been treated with an intravenous dose of 20 mg/kg. This study result is consistent with the known effects of fluoroquinolones on skeletal development (see "Pregnancy and lactation"). There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

INDICATIONS:
Moxifloxacin film-coated tablets are indicated for the treatment of the following bacterial infections caused by susceptible strains:

• Respiratory tract infections:

Acute Bacterial Sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis.*

Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus, or Moraxella catarrhalis.*

Community Acquired Pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Moraxella catarrhalis.*

• Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus or Streptococcus pyogenes*

• Complicated skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae or Enterobactercioacae.*

• 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.

Flonoxin film-coated 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 (eg. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae .

Flonoxin film-coated tablets are indicated for the treatment of the above infections if they are caused by bacteria susceptible to moxifloxacin.

RECOMMENDED DOSAGE:
Dose (adults):
The recommended dose for Flonoxin is 400 mg once daily (1 film coated tablet) for the above-mentioned indications and should not be exceeded.

For complicated skin and skin structure infections, therapy should usually be initiated with intravenous formulation. When switching from intravenous to oral dosage administration, no dosage adjustment is necessary.

Duration of treatment:
The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations are made:

• Acute exacerbation of chronic bronchitis: 5 days
• Acute sinusitis: 7 days
• Uncomplicated skin and skin structure infections: 7 days
• Community acquired pneumonia (mild to moderate in severity): 10 days
• Community acquired pneumonia: total recommended duration for sequential administration (intravenous followed by oral therapy) is 7-14 days
• Complicated skin and skin structure infections: total treatment duration for sequential therapy (intravenous followed by oral therapy) is 7-21 days
• Mild to moderate pelvic inflammatory disease: 14 days

The recommended duration of treatment for the indication being treated should not be exceeded.

Missed dose:
If a dose is missed, it should be taken anytime but not later than 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Additional information on special populations:
Children and adolescents
Efficacy and safety of Flonoxin in children and adolescents have not been established.
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 dosage adjustment is required in patients with mild or moderate impaired liver function. The use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).
Patients with renal impairment
No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. hemodialysis and continuous ambulatory peritoneal dialysis.

ROUTE OF ADMINISTRATION:
For oral administration only. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

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 data, moxifloxacin is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminase increase > 5fold ULN.

WARNINGS AND PRECAUTIONS:
Hypersensitivity
In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately.

Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases, the treatment with Flonoxin has to be discontinued, medical treatment (e.g., treatment for shock) is required.

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

Cardiac disorders
Flonoxin, has been shown to prolong the QT interval of the electrocardiogram in some patients. As 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 susceptible to drug-associated effects on the QT interval.

As the magnitude of QT prolongation may increase with increasing concentrations of the drug, the recommended dose and infusion rate (400mg within 60 minutes) should not be exceeded. However, in patients suffering from pneumonia, no correlation between plasma concentrations of moxifloxacin and QTc prolongation was observed. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade des pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Flonoxin treatment in clinical studies with more than 9000 patients, however, certain predisposing conditions may increase the risk for ventricular arrhythmias.

Therefore, treatment with Flonoxin should be avoided due to the lack of clinical experience with the drug in these patient populations:
• In patients with known prolongation of the QT interval
• In patients with uncorrected hypokalemia
• In patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents

Flonoxin should be used with caution as an additive effect of moxifloxacin on the QT interval cannot be excluded for the following conditions:
• In patients treated concomitantly with drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants
• In patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.
• In patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.
• In women and elderly patients who, both, may be more susceptible to QTc-prolonging drugs.

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.

Hepatobilliary system
Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with Flonoxin (see "Undesirable Effects"). Patients should be advised to contact their doctor immediately prior to continuing treatment if signs and symptoms fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
Due to limited clinical data the use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).

Seizures
Seizures may occur with fluoroquinolone therapy. Moxifloxacin should be used with caution in patients with known or suspected Central Nervous System (CNS) disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), which may predispose to seizures or lower the seizure threshold.

Disabling and potentially irreversible serious adverse reactions
Fluoroquinolones, including Flonoxin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue Flonoxin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including Flonoxin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Because of the widespread and rising prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, the addition of an appropriate antibiotic which is regularly active against N gonorrhoeae (e.g.a cephalosphorin) to empirical moxifloxacin therapy, should be considered.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral may occur with fluoroquinolone therapy including moxifloxacin, even within the first 48 hours of treatment. Cases occuring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and patients with solid organ transplants. At the first sign of tendinitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercises should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued.

Consult your doctor immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon. Tendon inflammation and rupture may occur even up to several months after discontinuing quinolone therapy including moxifloxacin.

Aortic aneurysm or dissection and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.
Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing
- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

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

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Exacerbation of Myasthenia Gravis
Fluoroquinolones, including moxifloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis.

Post-marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid moxifloxacin in patients with a known history of myasthenia gravis.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Gastrointestinal system
Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission.

Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

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

Skin and appendages
Fluoroquinolones have been shown to cause photosensitivity in patients. However, in specially designed pre-clinical and clinical studies photosensitivity has not been observed with Flonoxin. In addition, since first marketed there has been no clinical evidence that Flonoxin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight. If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

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.

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.

Complicated pelvic inflammatory disease
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 Flonoxin 400 mg film-coated tablets is not recommended.

MRSA infections
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.

Interaction with tests
Moxifloxacin in vitro activity may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Flonoxin.

Peripheral neuropathy
Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including Flonoxin. Symptoms may occur soon after initiation of Flonoxin and may be irreversible. Flonoxin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation.

Psychiatric adverse reactions
Fluoroquinolones, including Flonoxin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving Flonoxin, discontinue Flonoxin immediately and institute appropriate measures.

Genital tract infections
Because of the widespread and rising prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone-resistant N. gonorrhoeae can be excluded. If fluoroquinolone-resistant N. gonorrhoeae cannot be excluded, the addition of an appropriate antibiotic which is regularly active against N. gonorrhoeae (e.g., a cephalosporin) to empirical moxifloxacin therapy, should be considered.

Blood glucose disturbances
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Flonoxin. In Flonoxin-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue Flonoxin and initiate appropriate therapy immediately.

INTERACTIONS WITH OTHERS MEDICAMENTS:
For the following substances absence of a clinically relevant interaction with Flonoxin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Antacids, minerals and multi-vitamins
Concomitant ingestion of Flonoxin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug 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 and other preparations containing magnesium or aluminium, 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.

Warfarin
No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR *(International Normalized Ratio)*: Cases of increased anticoagulant activity have been reported in patients receiving anticoagulants concurrently with antibiotics, including Flonoxin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between Flonoxin and warfarin was not demonstrated in clinical trials, 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 moxifloxacin and vice versa. After repeated dosing in healthy volunteers moxifloxacin increased Cmax of

digoxin by approximately 30 % at steady state without affecting AUC or trough levels.

Charcoal

Concomitant dosing of charcoal and 400 mg oral Flonoxin reduced the systemic availability of the drug by more than 80 % by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinal is only slightly reduces systemic exposure (approx. 20%).

Food and dairy products

Absorption of moxifloxacin was not altered by food intake (including dairy products). Therefore, Flonoxin can be taken independent from food intake.

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 (eg. Quinidine, hydroquinone, 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 (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil)

USE IN PREGNANCY AND LACTATION:

Pregnancy:
The safe use of Flonoxin in human pregnancy has not been established. Reversible joint injuries are described in children receiving some fluoroquinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.

Consequently, the use of Flonoxin during pregnancy is contraindicated.

Lactation:
As with other fluoroquinolones, Flonoxin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of Flonoxin in nursing mothers is contraindicated.

EFFECTS ON ABILITY TO DRIVE OR USE MACHINES:

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders.

SIDE EFFECTS/ADVERSE REACTIONS:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhea.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are de¬fined as:
• common (≥ 1/100 to < 1/10)
• uncommon (≥ 1/1,000 to < 1/100)
• rare (≥ 1/10,000 to < 1/1,000)
• very rare (< 1/10,000)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations	Mycotic super-infections				
Blood and the lymphatic system disorders		Anemia Leukopenia(s) Neutropenia Thrombocytopenia Thrombocythemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal	
Immune system disorders		Allergic reaction Pruritus Rash Urticaria Blood eosinophilia	Anaphylactic / anaphylactoid reaction Allergic edema / angioedema (incl. laryngeal edema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)	
Metabolism and nutrition disorders		Hyperlipidemia	Hyperglycemia Hyperuricemia	Hypoglycemia	
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity / agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts) Hallucinations	Depersonalization Psychotic reactions, (potentially culminating in self-injurious behavior, such as suicidal ideation / thoughts or suicide attempts)	
Nervous system disorders	Headache Dizziness	Par- and Dysesthesia Taste disorders (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorders Tremor Vertigo Somnolence	Hypoesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; in very rare cases leading to fall with injuries, esp. in elderly) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia	Hyperesthesia	Peripheral neuropathy (that may be irreversible) and polyneuropathy
Eye disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)	
Ear and labyrinth disorders			Tinnitus Hearing impairment including deafness (usually reversible)		
Cardiovascular system disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachy-arrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes * Cardiac arrest * * (especially in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia)	
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 Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)		
Hepato-biliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-trans-ferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)	
Skin and subcutaneous tissue disorders				Bullous skin reactions like Stevens-John-son-Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Tendon rupture Arthritis Gait disturbance (caused by muscular, tendon or joint symptoms) Exacerbation of symptoms of myasthenia gravis	
Renal and urinary disorders		Dehydration (caused by diarrhea or reduced fluid intake)	Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)		
General disorders and administration site conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Edema		

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:
Common: Increased gamma-glutamyl-transferase
Uncommon: Ventricular tachyarrhythmias, Hypotension, Edema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (incl. grand mal convulsions), Hallucination, Renal impairment and renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)

Post Marketing Experience
Exacerbation of Myasthenia Gravis

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

Only limited data on overdose are available. Single doses of up to 1200 mg and multiple doses of 600mg moxifloxacin over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. The use of charcoal early after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of overdosage.

STORAGE CONDITIONS:
Store in a dry place below 30°C.
Store in original package to protect from moisture.
Keep out of reach of children.
Jauhkan daripada kanak-kanak.

LIST OF EXCIPIENTS:
Film coated tablets:
Core tablet:
Lactose Monohydrate 200 Mesh, Croscarmellose Sodium, Povidone 30, Isopropyl Alcohol, Magnesium Stearate.

Film-coating:
The tablets are film-coated with a mixture of Hypromellose, Titanium Dioxide, Macrogol, Iron Oxide Red

PACKING/ PACK SIZES:
1 x 5 tablets in ALU-PVC/ALU/OPA pack
2 x 5 tablets in ALU-PVC/ALU/OPA pack

SHELF LIFE:
Please refer to outer package.

PRODUCT REGISTRATION HOLDER (MALAYSIA):
Duopharma Marketing Sdn. Bhd.
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia.

PRODUCT REGISTRATION HOLDER (SINGAPORE):
Duopharma (Singapore) Pte. Ltd.
25, International Business Park,
#03-53 German Centre,
Singapore 609916

MANUFACTURER:
Duopharma Manufacturing (Bangi) Sdn. Bhd.
Lot No. 2 & 4, Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia.

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