

SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITE AND TENDON FRACTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND VIOLENCE OF MYASTHENIA GRAVIS

- Fluoroquinolones, including MULTIFLEX MOXIFLEX, can cause disabling and irreversible adverse reactions such as:
 - Tendinitis and tendon rupture
 - Peripheral neuropathy
 - Central nervous system effects

In patients with any of these reactions, the use of MULTIFLEX MOXIFLEX should be discontinued immediately and the use of fluoroquinolone should be avoided.

- Fluoroquinolones, including MULTIFLEX MOXIFLEX, may aggravate muscle weakness in patients with myasthenia gravis. The use of MULTIFLEX MOXIFLEX should be avoided in patients with a known history of myasthenia gravis.
- Since fluoroquinolone group drugs including MULTIFLEX MOXIFLEX are known to be associated with serious adverse reactions, they can be used in the following indications if there is no other alternative.
 - Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT

MULTIFLEX MOXIFLEX 400 mg/250 mL I.V. Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Moxifloxacin 400 mg (as hydrochloride)

Excipients:

Sodium chloride 2.0 g

(250 mL of solution for infusion contains 34 mmol sodium.)

Sodium hydroxide (for pH adjustment)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

250 mL polypropylene bag containing 250 mL of yellow-clear solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluoroquinolones, including MULTIFLEX MOXIFLEX, should not be used because of the risk of serious adverse effects in the presence of alternative treatment options for acute

bacterial exacerbation of chronic bronchitis.

Official guidelines on the correct use of antibacterial drugs should be considered. MULTIFLEX MOXIFLEX should only be used for the treatment of infections that have been proven to be susceptible to susceptible bacteria, or where there is serious suspicion.

MULTIFLEX MOXIFLEX is indicated for the treatment of the following bacterial infections caused by susceptible strains.

- **Acute exacerbation of chronic bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*;
- *Streptococcus pneumoniae* (including penicillin-resistant strains with MIC of $\geq 2 \mu\text{g} / \text{ml}$ for penicillin), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumonia* **from the community**; including community-acquired pneumonia caused by multidrug-resistant strains *;
- **Streptococcus pneumoniae* with multiple drug resistance, such as penicillin-resistant *S. Pneumoniae* strains and strains resistant to two or more of the following antibiotics: penicillin (MIC $\geq 2 \mu\text{g} / \text{ml}$), 2nd generation cephalosporins (eg, cefuroxime), macrolides, tetracyclines and trimethoprim / sulfamethoxazole.
- **In uncomplicated skin and soft tissue infections** caused by *Staphylococcus aureus*, *Streptococcus pyogenes*;
- **Complicated skin and soft tissue infections (including diabetic foot)** caused by methicillin-sensitive *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*;
- **In complicated intraabdominal infections** (including polymicrobial infections such as abscesses) caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron* or *Peptostreptococcus species*

Official guidelines on the appropriate use of antibacterial agents should be considered.

4.2 Posology and method of administration

Posology:

For the above indications, MULTIFLEX MOXIFLEX is administered once daily (250 mL) and this dose should not be exceeded.

Administration frequency and duration:

The duration of treatment should be determined by the severity of the indication or the clinical response. The following general recommendations are made for the treatment of upper and lower respiratory infections:

In clinically indicated cases, treatment can be started with intravenous administration and continued with oral film-coated tablet administration.

Acute exacerbation in chronic bronchitis: 5 days

Community-acquired pneumonia: Recommended treatment duration for sequential administration (oral administration following intravenous administration): 7-14 days

Uncomplicated skin and soft tissue infections: 7 days

Sequential treatment time for complicated skin and soft tissue infections (oral administration following intravenous administration): 7-21 days.

Sequential treatment for complicated intraabdominal infections (oral administration following intravenous administration): 5-14 days.

The duration of treatment should not be exceeded for the indication being treated. MULTIFLEX MOXIFLEX has been studied in clinical trials (complicated skin and soft tissue infections) for up to 21 days of treatment.

Method of Administration:

Infusion time for intravenous administration is 60 minutes.

The infusion solution can be administered directly or with a T-tube together with infusion solutions to which it is compatible.

The following solutions were found to form stable mixtures at room temperature for 24 hours by co-administration with MULTIFLEX MOXIFLEX and were found to be compatible with MULTIFLEX MOXIFLEX.

- Water for injection
- 0.9% sodium chloride
- 1 molar sodium chloride
- 5% Glucose
- 10% Glucose
- 40% Glucose
- 20% Xylitol
- Ringer's Solution

- Ringer Lactate Solution

If MULTIFLEX MOXIFLEX is to be co-administered with another drug, the two drugs should be administered separately. Only clear solutions should be used.

Additional information on specific populations

Renal / hepatic impairment:

No dose adjustment is required in patients with renal impairment (including creatinine clearance ≥ 30 mL/min/1.73m²) and in chronic dialysis patients such as hemodialysis and continuous ambulatory peritoneal dialysis.

Insufficient data are available in patients with hepatic dysfunction (see section 4.3).

Pediatric population:

The efficacy and safety of MULTIFLEX MOXIFLEX in children and adolescents has not been established. (see also Section 4.3).

Geriatric population:

No dosage adjustment is required for the elderly.

Other:

No dose adjustment is required in ethnic groups

4.3 Contraindications

- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- 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 (see also section 4.5).

Due to limited clinical data, moxifloxacin is also contraindicated in patients with severe hepatic impairment (Child Pugh C) and in patients with increased transaminase levels greater than 5 times the upper limit of normal.

4.4 Special warnings and precautions for use

Serious and potentially irreversible adverse reactions with disability, including tendonitis and tendon rupture, peripheral neuropathy and central nervous system effects

Fluoroquinolones, including MOXIFLEX, have been associated with serious irreversible and potentially irreversible serious adverse reactions. Common adverse reactions include musculoskeletal and peripheral nervous system (tendonitis, tendon rupture, tendon swelling or inflammation, tingling or numbness, numbness of arms and legs, muscle pain, muscle weakness, joint pain, swelling of joints), arthralgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendency, insomnia, severe headache, and confusion) (see section 4.8).

These reactions can be seen within hours or weeks after starting MULTIFLEX MOXIFLEX. Patients of all age groups or without pre-existing risk factors have experienced these adverse reactions.

MULTIFLEX MOXIFLEX should be discontinued immediately if the first signs or symptoms of any serious adverse reactions occur. Furthermore, the use of fluoroquinolones, including MULTIFLEX MOXIFLEX, should be avoided in patients experiencing any of these serious adverse reactions in connection with fluoroquinolones.

Acute bacterial exacerbation of chronic bronchitis should be preferred when treatment with another agent is not possible.

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not be exceeded. For more details see below and refer to sections 4.3 and 4.5.

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 ischaemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. (See also sections 4.3 and 4.5.)

Moxifloxacin should be used with caution in patients who are taking medications that can reduce potassium levels. (See also sections 4.3 and 4.5.)

Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia. (See also section 4.3.)

Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as moxifloxacin and therefore special caution is required.

Hypersensitivity/allergic reactions

Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In cases of clinical manifestations of severe hypersensitivity reactions moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). 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.

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Patients predisposed to seizures

Quinolones are known to trigger seizures. Use should be with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.

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 a potentially irreversible condition (see section 4.8).

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, moxifloxacin should be discontinued, and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

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 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.

Patients with myasthenia gravis

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

Exacerbation of Myasthenia Gravis:

Fluoroquinolones have neuromuscular blockade activity and may exacerbate muscle weakness in patients with myasthenia gravis. In patients with myasthenia gravis using fluoroquinolone, severe post-marketing adverse events involving ventilatory support and death have been associated with fluoroquinolone. Patients with a history of myasthenia gravis should avoid the use of fluoroquinolone (see section 4.8).

Tendon inflammation, tendon rupture

With quinolone therapy, including moxifloxacin, tendon inflammation and rupture (especially the Achilles tendon) can develop even within 48 hours after the start of treatment; cases occurring months after the end of treatment have been reported. The risk of tendinitis and tendon rupture is increased in elderly patients using concomitant corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin, rest the affected limb, and seek immediate medical advice (eg immobilization) to begin treatment of the affected tendon (see sections 4.3 and 4.8).

Patients with renal impairment

Elderly patients with kidney disorders should use moxifloxacin carefully if they cannot maintain sufficient fluid intake, because dehydration may increase the risk of kidney failure.

Vision disorders

If visual impairment or any problems with the eyes occur, an ophthalmologist should be consulted immediately.

Dysglycemia

As with all fluoroquinolones, disturbances in blood glucose levels, including hypoglycemia and hyperglycemia, have been reported with MULTIFLEX MOXIFLEX. Dysglycemia in patients receiving MULTIFLEX MOXIFLEX therapy has predominantly occurred in elderly diabetic patients receiving concomitant oral hypoglycemic medication (eg sulphonylurea) or insulin therapy. Careful monitoring of blood glucose levels is recommended in diabetic patients (see section 4.8).

Prevention of photosensitivity reactions

Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk of inducing photosensitivity. However, patients should be advised not to be exposed to severe UV radiation or sunlight during treatment with moxifloxacin.

Patients with glucose-6-phosphate dehydrogenase deficiency

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

Peri-arterial tissue inflammation

Moxifloxacin is used only intravenously. Intra-arterial administration should be avoided as preclinical studies show peri-arterial tissue inflammation following intra-arterial infusion.

Patients with special cSSSI

The clinical efficacy of moxifloxacin in the treatment of diabetic foot with severe burn infections, fasciitis and osteomyelitis has not been proven.

Interference with biological tests

Moxifloxacin suppresses mycobacterial growth and *Mycobacterium* spp. May interfere with the culture test. For this reason, moxifloxacin may cause false negative results in samples taken from patients ongoing treatment.

Patients with MRSA infections

The use of moxifloxacin is not recommended in the treatment of MRSA infections. If MRSA infection is suspected or the diagnosis is confirmed, treatment with an appropriate antibacterial agent should be initiated (see section 5.1).

Paediatric population

Due to adverse effects on the cartilage in juvenile animals (see section 5.3) the use of moxifloxacin in children and adolescents < 18 years is contraindicated (see section 4.3).

Epidemiological studies report an increased risk of aortic aneurysm and dissection, especially in the elderly population, after fluoroquinolone use. Therefore, fluoroquinolones may be used in patients with positive family history of aneurysm disease, patients with a previous diagnosis of aortic aneurysm and / or aortic dissection, patients with other risk factors or predisposing conditions for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis) should only be used after a careful benefit / risk assessment and other therapeutic options have been considered. In case of sudden abdominal, chest or back pain, patients should be advised to seek immediate medical attention.

Use in patients on a sodium diet

This medicinal product contains 787 mg (approximately 34 mmol) sodium per dose. This should be taken into account for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with medicinal products

An additive effect on QT interval prolongation of MULTIFLEX MOXIFLEX 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 MULTIFLEX MOXIFLEX with any of the following medicinal products is contraindicated (see also section 4.3):

- anti-arrhythmics class IA (e.g., quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g., amiodarone, sotalol, dofetilide, ibutilide)
- antipsychotics (e.g., phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels (e.g., loop and thiazide-type diuretics, laxatives and enemas [high doses],

corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

After repeated dosing in healthy volunteers, moxifloxacin increased C_{\max} of digoxin by approximately 30% without affecting AUC or trough levels. No precaution is required for use with digoxin.

In studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of glibenclamide. The combination of glibenclamide and moxifloxacin could theoretically result in a mild and transient hyperglycaemia. However, the observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore, no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

Changes in INR (International Normalised Ratio):

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. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Under these circumstances, it is difficult to evaluate whether the infection or the treatment caused the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole. *In vitro* studies with human cytochrome P450 enzymes supported these findings. Considering these results, a metabolic interaction via cytochrome P450 enzymes is unlikely.

Interaction with food:

Moxifloxacin has no clinically relevant interaction with food including dairy products.

Additional information for special populations:

Pediatric population:

The efficacy and safety of MULTIFLEX MOXIFLEX in children and adolescents has not been established (see also Section 4.3).

4.6 Pregnancy and lactation

General advice

Pregnancy category:C

Women with childbearing potential / Contraception:

Studies on animals do not indicate impairment of fertility (see section 5.3).

Pregnancy

The safety of MULTIFLEX MOXIFLEX in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity (see section 5.3). 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, MULTIFLEX MOXIFLEX must not be used in pregnant women (see section 4.3).

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 (see section 4.3).

Reproductive ability / Fertility

Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g., dizziness; acute, transient loss of vision, see section 4.8) or acute and short-lasting loss of consciousness (syncope, see section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects

Adverse reactions observed in clinical trials and derived from post-marketing reports with moxifloxacin 400 mg daily administered by the intravenous or oral route (intravenous only, sequential [IV/oral] and oral administration) sorted by frequencies are listed below:

Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$),

Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$),

Very rare ($< 1/10,000$)

Unknown (cannot be estimated from the available data)

Infections and infestations

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

Blood and lymphatic system disorders

Uncommon: Anaemia, Leucopenia(s), Neutropenia, Thrombocytopenia, Thrombocythemia, Blood eosinophilia

Rare: Abnormal thromboplastin level

Very rare: Prothrombin time prolonged/ INR increased, Agranulocytosis

Immune system disorders

Uncommon: Allergic reaction (see section 4.4)

Rare: Anaphylaxis incl. very rarely life-threatening shock (see section 4.4)

Allergic oedema/ angiooedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)

Metabolism and nutrition disorders

Uncommon: Hyperlipidemia

Rare: Hyperglycemia, Hyperuricemia

Very Rare: Hypoglycemia

Psychiatric disorders

Uncommon: Anxiety reactions, psychomotor hyperactivity/ agitation

Rare: Emotional lability, Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4), hallucination

Very Rare: Depersonalization, Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts, see section 4.4)

Nervous system disorders

Common: headache, dizziness

Uncommon: Paraesthesia / Dysesthesia, taste disturbances (including loss of taste in very rare cases), confusion and disorientation, sleep disturbances (usually insomnia), tremors, vertigo, somnolence

Rare: Hypoaesthesia, olfactory disturbances (including loss of sense of smell), abnormal dreams, coordination disorder (including gait disturbances especially caused by dizziness or vertigo), seizures of various clinical manifestations (including grand mal convulsions), attention disorder, speech disorders, amnesia, peripheral neuropathy, and polyneuropathy

Very rare: Hyperesthesia.

Eye disorders

Uncommon: Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)

Very Rare: Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7)

Ear and labyrinth disorders

Rare: Tinnitus, Hearing impairment including deafness (usually reversible)

Cardiac disorders

Common: QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)

Uncommon: QT prolongation (see section 4.4), Palpitations, Tachycardia, Atrial fibrillation, Angina pectoris

Rare: Ventricular tachyarrhythmias, Syncope (i.e., acute and short lasting loss of consciousness)

Very Rare: Unspecified arrhythmias, Torsade de Pointes (see section 4.4), Cardiac arrest (see section 4.4)

Vascular disorders

Uncommon: Vasodilatation

Rare: Hypertension, Hypotension

Very Rare: Vasculitis

Respiratory, thoracic and mediastinal disorders

Yaygın olmayan: Dyspnea (including asthmatic conditions)

Gastrointestinal disorders

Common: Nausea, Vomiting, Gastrointestinal and abdominal pains, Diarrhoea

Uncommon: Decreased appetite and food intake, Constipation, Dyspepsia, Flatulence, Gastritis, Increased amylase

Rare: Dysphagia, Stomatitis, Antibiotic-associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications, see section 4.4)

Hepatobiliary disorders

Common: Increase in transaminases

Uncommon: Hepatic impairment (incl. LDH increase), Increased bilirubin, Increased gamma-glutamyl-transferase, Increase in blood alkaline phosphatase

Rare: Jaundice, Hepatitis (predominantly cholestatic)

Very Rare: Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases, see section 4.4)

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, Rash, Urticaria, Dry skin

Very Rare: Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4)

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, Myalgia

Rare: Tendonitis (see section 4.4), Muscle cramp, Muscle twitching, Muscle weakness

Very Rare: Tendon rupture (see section 4.4), Arthritis, Muscle rigidity, Exacerbation of symptoms

of myasthenia gravis (see section 4.4)

Renal and urinary disorders

Uncommon: Dehydration

Rare: Renal impairment (incl. increase in BUN and creatinine), Renal failure (see section 4.4)

General disorders and administration site conditions

Common: Injection and infusion site reactions

Uncommon: Feeling unwell (predominantly asthenia or fatigue), Painful conditions (incl. pain in back, chest, pelvic and extremities), Sweating, Infusion site (thrombo-) phlebitis

Rare: Oedema

The following undesirable effects have a higher frequency category in the subgroup of IV treated patients with or without subsequent oral therapy:

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrhythmias, hypotension, oedema, antibiotic-associated colitis (incl. pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4), seizures incl. grand mal convulsions (see section 4.4), hallucination, renal impairment (incl. increase in BUN and creatinine), renal failure (see section 4.4)

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 (see section 4.4)

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

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 400 mg 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. Only limited data on overdose are available. Healthy volunteers received single doses of up to 1200 mg and repeated doses of 600 mg of moxifloxacin for 10 days without any significant adverse effects. In case of overdose, it is recommended that ECG measurements, together with appropriate supportive therapy as required by the patient's clinical condition, be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones,

ATC code: J01MA14

Mechanism of action

Moxifloxacin inhibits bacterial type II topoisomerase (DNA gyrase and topoisomerase IV) activity. Topoisomerases provide DNA replication, repair and transcription.

PK/PD

Fluoroquinolones exhibit a concentration dependent killing of bacteria. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials indicate that the primary determinant of efficacy is the AUC₂₄/MIC ratio.

Mechanism of resistance

Resistance to fluoroquinolones can arise through mutations in DNA gyrase and topoisomerase IV. Other mechanisms may include over-expression of efflux pumps, impermeability, and protein-mediated protection of DNA gyrase. Cross resistance should be expected between moxifloxacin and other fluoroquinolones.

The activity of moxifloxacin is not affected by mechanisms of resistance that are specific to antibacterial agents of other classes.

Breakpoints

EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2012):

Organism	Susceptible	Resistant
<u><i>Staphylococcus spp.</i></u>	≤0.5 mg/L ≥24 mm	>1 mg/ L <21 mm
<u><i>S. pneumoniae</i></u>	≤0.5 mg/ L ≥22 mm	>0.5 mg/ L <22 mm
<u><i>Streptococcus</i> Groups A, B, C, G</u>	≤0.5 mg/ L ≥18 mm	>1 mg/ L <15 mm
<u><i>H. influenza</i></u>	≤0.5 mg/ L ≥25 mm	>0.5 mg/ L ≥25 mm
<u><i>M. catarrhalis</i></u>	≤0.5 mg/ L ≥23 mm	>0.5 mg/ L <23 mm
<u><i>Enterobacteriaceae</i></u>	≤0.5 mg/ L ≥20 mm	>1 mg/ L <17 mm
<u>Non-species related breakpoints*</u>	≤0.5 mg/ L	>1 mg/ L
*Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined.		

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
<u>Aerobic Gram-positive micro-organisms</u> <i>Staphylococcus aureus</i> *+ <i>Streptococcus agalactiae</i> (Group B) <i>Streptococcus milleri</i> group* (<i>S. anginosus</i> , <i>S. constellatus</i> ve <i>S. intermedius</i>) <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> *(Group A) <i>Streptococcus viridans</i> grup (<i>S. viridans</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>S. sanguinis</i> , <i>S. salivarius</i> , <i>S. thermophilus</i>)
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> <i>Haemophilus influenzae</i> * <i>Legionella pneumophila</i> <i>Moraxella (Branhamella) catarrhalis</i> *
<u>Anaerobic micro-organisms</u> <i>Prevotella spp.</i>

<u>“Other” micro-organisms</u> <i>Chlamydophila (Chlamydia) pneumoniae</i> * <i>Coxiella burnetii</i> <i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> * <i>Enterococcus faecium</i> *
<u>Aerobic Gram-negative micro-organisms</u> <i>Enterobacter cloacae</i> * <i>Escherichia coli</i> *# <i>Klebsiella pneumoniae</i> *# <i>Proteus mirabilis</i> *
<u>Anaerobic micro-organisms</u> <i>Bacterioides fragilis</i> *
Inherently resistant organisms
<u>Aerobic Gram-negative micro-organisms</u> <i>Pseudomonas aeruginosa</i>

*Activity has been satisfactorily demonstrated in clinical studies.

+Methicillin resistant *S. aureus* have a high probability of resistance to fluoroquinolones.

Moxifloxacin resistance rate of > 50% have been reported for methicillin resistant *S. aureus*.

#ESBL-producing strains are commonly also resistant to fluoroquinolones.

5.2 Pharmacokinetic properties

General Particulars

Absorption and Bioavailability

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

In patients, there is no need for age or gender related dose adjustment on intravenous moxifloxacin. Pharmacokinetics are linear in the range of 50 - 1200 mg single oral dose, up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

Distribution

Moxifloxacin is distributed to extravascular spaces rapidly. The steady-state volume of distribution (V_{ss}) is approximately 2 l/kg. *In vitro* and *ex vivo* experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound

to serum albumin.

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

Biotransformation

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal (approximately 40%) and biliary/faecal (approximately 60%) pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

In clinical Phase I and *in vitro* studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism.

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. Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose (unchanged drug and metabolites) totalled to approximately 98% after intravenous administration of the drug. Renal clearance amounted to about 24 - 53 mL/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Characteristics in patients

Renal failure

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance $> 20 \text{ mL/min/1.73 m}^2$). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of $< 30 \text{ mL/min/1.73 m}^2$).

Hepatic failure

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. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

5.3 Preclinical safety data

In conventional repeated dose studies moxifloxacin revealed haematological and hepatic toxicity in rodents and non-rodents. Toxic effects on the CNS were observed in monkeys. These effects occurred after the administration of high doses of moxifloxacin or after prolonged treatment.

In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/L caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

After intravenous administration findings indicative of systemic toxicity were most pronounced when moxifloxacin was given by bolus injection (45 mg/kg) but they were not observed when moxifloxacin (40 mg/kg) was given as slow infusion over 50 minutes.

After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

Moxifloxacin was genotoxic in *in vitro* tests using bacteria or mammalian cells. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

In vitro, moxifloxacin revealed cardiac electrophysiological properties that can cause prolongation of the QT interval, even though at high concentrations.

After intravenous administration of moxifloxacin to dogs (30 mg/kg infused over 15, 30 or 60 minutes) the degree of QT prolongation was clearly depending on the infusion rate, i.e. the shorter the infusion time the more pronounced the prolongation of the QT interval. No prolongation of the QT interval was seen when a dose of 30 mg/kg was infused over 60 minutes.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase

in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations. Quinolones, including moxifloxacin, are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injection

6.2 Incompatibilities

The following solutions are incompatible with MOXIFLEX solution for infusion:

10% Sodium chloride

20% Sodium chloride

4.2% Sodium hydrogen carbonate

8.4% Sodium hydrogen carbonate

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep at room temperature below 25° C.

At cool storage temperatures (below 15° C), redissolution precipitation may occur at room temperature.

Therefore, it is not recommended to store MULTIFLEX MOXIFLEX in the refrigerator.

Store in original packaging.

6.5 Nature and contents of container

In 250 ml PP bag with two outputs with protective Al overpouch.

6.6 Special precautions for disposal

Unused products or waste materials should be disposed of in accordance with the "Medical Waste

Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

HAYER FARMA İlaç A.Ş.

Akbaba Mah. Maraş Cad. No: 52/2/1

Beykoz / İSTANBUL

Phone: 0216 324 38 38

Fax: 0216 317 04 98

E-posta: info@hayer.com.tr

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