SUMMARY OF PRODUCT CHARACTERISTICS

MOXIFLOXACIN (HYDROCHLORIDE) TABLETS 400 mg

(Moxifloxacin Hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

MOXIFLOXACIN TABLETS 400 mg (Moxifloxacin Hydrochloride)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Moxifloxacin Hydrochloride Ph. Eur

Equivalent to Moxifloxacin……400 mg

Excipients with known effect: contains 5.0 mg anhydrous lactose and 230.17 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dull red colored, Capsule shaped, bevelled, film coated tablets, debossed with "M400" on one side and breakline on other side.

4. CLINICAL PARTICULARS [1, 2]

4.1 Therapeutic indications

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Moxifloxacin tablets and other antibacterial drugs, moxifloxacin hydrochloride should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Moxifloxacin Hydrochloride Tablet 400 mg is indicated for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below (see **Posology and method of administration** and **Special warnings and precautions for use**)

Culture and Susceptibility Testing

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 moxifloxacin hydrochloride (see **PHARMACOLOGICAL PROPERTIES**). Therapy with moxifloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy

should be continued.

Moxifloxacin hydrochloride should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections or when these have failed.

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,* methicillin-susceptible *Staphylococcus aureus,* or *Moraxella catarrhalis.*

Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains*), *Haemophilus influenzae, Moraxella catarrhalis,* methicillin-susceptible *Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* or *Chlamydophilia pneumoniae*.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (minimum inhibitory concentrations [MIC] ≥2 mcg/mL), 2nd generation cephalosporins (for example, cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Uncomplicated Skin and Skin Structure Infections caused by methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*

Moxifloxacin Tablets 400 mg should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

Complicated Skin and Skin Structure Infections caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* or *Enterobacter cloacae.*

Complicated Intra-Abdominal Infections including polymicrobial infections such as abscess caused by *Escherichia coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron,* or *Peptostreptococcus* species.

Mild to Moderate Pelvic Inflammatory Disease (i.e infections of female upper genital tract, including salpingitis and endometritis) without an associated tubo-ovarian or pelvic abscess

Moxifloxacin Tablets 400 mg are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin hydrochloride resistance of *Neisseria gonorrhoeae* unless moxifloxacin hydrochloride -resistant *Neisseria gonorrhoeae* can be excluded (see **Special warnings and precautions for use**).

4.2 Posology and method of administration

Dosage in Adult Patients

The dose of moxifloxacin hydrochloride is 400 mg (orally or as an intravenous infusion) once every 24 hours. The duration of therapy depends on the type of infection as described in the table below.

Table: Dosage and Duration of Therapy in Adult Patients

Type of Infection [a]	**Dose Every 24 hours**	**Duration** [b] **(days)**
Acute Bacterial Sinusitis	400 mg	10
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5
Community Acquired Pneumonia	400 mg	7-14
Uncomplicated Skin and Skin Structure Infections	400 mg	7
Complicated Skin and Skin Structure Infections	400 mg	7 - 21
Complicated Intra-Abdominal Infections	400 mg	5-14
Mild to Moderate Pelvic InflammatoryDisease	400 mg	14

[a] due to the designated pathogens (see **Therapeutic indications**)

[b] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician

Intravenous formulation is indicated when it offers a route of administration advantageous to the patient (for example, patient cannot tolerate an oral dosage form). When switching from intravenous to oral formulation, no dosage adjustment is necessary. Patients whose therapy is started with moxifloxacin hydrochloride IV may be switched to moxifloxacin tablets when clinically indicated at the discretion of the physician.

Oral doses of moxifloxacin hydrochloride should be administered at least 4 hours before or 8 hours after products containing magnesium, aluminum, iron or zinc, including antacids, sucralfate, multivitamins and didanosine chewable/buffered tablets or the pediatric powder for oral solution.

Moxifloxacin hydrochloride can be taken with or without food, drink fluids liberally.

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

Renal Impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis (see **PHARMACOLOGICAL PROPERTIES**).

Hepatic Impairment

Due to limited clinical data, moxifloxacin hydrochloride is also contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5 fold ULN (see **Contraindications** and **Special warnings and precautions for use**).

Other Special Populations

No adjustment of dosage is required in the elderly and in patients with low bodyweight.

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

Children and Adolescents

Moxifloxacin hydrochloride is contraindicated in children and adolescents (< 18 years). Efficacy and safety of moxifloxacin in children and adolescents have not been established. Moxifloxacin hydrochloride causes arthropathy in juvenile animals (see **Contraindications**).

4.3 Contraindications

- Hypersensitivity to moxifloxacin hydrochloride, 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. Patients with impaired liver function (Child Pugh C) and in patients with transaminases increase > 5 fold ULN.
- Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin hydrochloride, in the form of QT prolongation. For reasons of drug safety, moxifloxacin hydrochloride 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 hydrochloride should not be used concurrently with other drugs that prolong the QT interval (see **Interaction with other medicinal products and other forms of interaction**).

4.4 Special warnings and precautions for use

WARNING:
Fluoroquinolones, including moxifloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Fluoroquinolones, including moxifloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid moxifloxacin in patients with known history of myasthenia gravis.

Tendinopathy and Tendon Rupture

Fluoroquinolones, including moxifloxacin hydrochloride, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the

Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Moxifloxacin hydrochloride should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug (see **Undesirable effects**).

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including moxifloxacin hydrochloride, hydrochloride have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid moxifloxacin hydrochloride in patients with known history of myasthenia gravis.

QT Prolongation

Moxifloxacin hydrochloride has been shown to prolong the QT interval of the electrocardiogram in some patients. Following oral dosing with 400 mg of moxifloxacin hydrochloride the mean (± SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 msec (± 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 10 msec (±22) on Day 1 (n=667) and 7 msec (± 24) on Day 3 (n = 667).

The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (for example, quinidine, procainamide) or Class III (for example, amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

Pharmacokinetic studies between moxifloxacin hydrochloride and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin hydrochloride and these drugs cannot be excluded; therefore caution should be exercised when moxifloxacin hydrochloride is given concurrently with these drugs. In reported premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin hydrochloride and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Moxifloxacin hydrochloride should be used with caution in patients with ongoing proarrhythmic

conditions (especially women and elderly patients), such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No excess in cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin hydrochloride treatment in over 15,500 patients in controlled clinical studies, including 759 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin hydrochloride tablet treated patients in a reported post-marketing observational study in which ECGs were not performed. Elderly patients using IV moxifloxacin hydrochloride may be more susceptible to drug-associated QT prolongation.

In addition, moxifloxacin hydrochloride should be used with caution in patients with mild, moderate, or severe liver cirrhosis (see **PHARMACOLOGICAL PROPERTIES** and ***Information for patients***).

If signs of cardiac arrhythmia occur during treatment with moxifloxacin hydrochloride, treatment should be stopped and ECG should be performed.

Medication that can reduce potassium level should be used with caution in patients receiving moxifloxacin hydrochloride.

Hypersensitivity Reactions

Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including moxifloxacin hydrochloride. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin hydrochloride 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 **Undesirable effects**).

Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including moxifloxacin hydrochloride. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- Fever, rash, or severe dermatologic reactions (for example, toxic epidermal necrolysis, Stevens-Johnson syndrome)
- Vasculitis; arthralgia; myalgia; serum sickness Allergic pneumonitis
- Interstitial nephritis; acute renal insufficiency or failure Hepatitis; jaundice; acute hepatic necrosis or failure
- Anemia including hemolytic and aplastic, thrombocytopenia including thrombotic

thrombocytopenic purpura, leucopenia, agranulocytosis, pancytopenia and/or other hematologic abnormalities

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

Central Nervous System Effects

Quinolones, including moxifloxacin hydrochloride, may cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia (see **Undesirable effects**).

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving moxifloxacin hydrochloride, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin hydrochloride should be used with caution in patients with known or suspected CNS disorders (for example, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (see **Undesirable effects** and **Interactions with other medicinal products and other forms of interactions**). In case of seizures, treatment with moxifloxacin hydrochloride should be discontinued and appropriate measures instituted.

Caution is recommended if moxifloxacin hydrochloride is to be used in psychotic patients or in patients with history of psychiatric disease.

Clostridium Difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including moxifloxacin hydrochloride, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated (see **Undesirable effects**).

Appropriate infection control measures should be undertaken to reduce the risk of transmission.

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

Peripheral Neuropathy

Rare 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 quinolones.

Patients under treatment with moxifloxacin hydrochloride 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 **Undesirable effects**).

Arthropathic Effects in Animals

The oral administration of moxifloxacin hydrochloride caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (for example, burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolone antibiotics after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs (see **Undesirable effects** and **PHARMACOLOGICAL PROPERTIES**).

Development of Drug Resistant Bacteria

Prescribing moxifloxacin hydrochloride in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Vision Disorders

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

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, moxifloxacin hydrochloride should be used with caution in these patients.

Patients with 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 moxifloxacin 400 mg film-coated tablets is not recommended.

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin hydrochloride should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin hydrochloride -resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Interference with Biological Tests

Moxifloxacin hydrochloride therapy may interfere with the *Mycobacterium spp*. culture test by suppression of mycobacterial growth causing false negative results.

Patients with MRSA Infections

Moxifloxacin hydrochloride 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 **PHARMACOLOGICAL PROPERTIES**).

Geriatric Patients

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as moxifloxacin hydrochloride. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing moxifloxacin hydrochloride to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue moxifloxacin hydrochloride and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (see **Undesirable effects**)

In reported controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin hydrochloride were greater than or equal to 65 years of age and 9% were greater than or equal to 75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of oral moxifloxacin hydrochloride in patients aged 65 or older compared to younger adults.

In trials of intravenous use, 42% of moxifloxacin hydrochloride patients were greater than or equal to 65 years of age, and 23% were greater than or equal to 75 years of age. The clinical trial data demonstrated that the safety of intravenous moxifloxacin hydrochloride in patients aged 65 or older was similar to that of comparator-treated patients. In general, elderly patients may be more susceptible to drug-associated effects of the QT interval. Therefore, moxifloxacin hydrochloride should be avoided in patients taking drugs that can result in prolongation of the QT interval (for example, class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (for example, known QT prolongation, uncorrected hypokalemia) (see **Interactions with medicinal products and other forms of interactions**).

Patients with Hepatic Impairment

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

Information for Patients

Antibacterial Resistance

Antibacterial drugs including moxifloxacin hydrochloride should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When moxifloxacin hydrochloride is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by moxifloxacin hydrochloride or other antibacterial drugs in the future.

Administration with Food, Fluids, and Drug Products Containing Multivalent Cations Patients should be informed that moxifloxacin tablets may be taken with or without food. Patients should be advised to drink fluids liberally. Moxifloxacin hydrochloride tablets should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate, or didanosine chewable/buffered tablets or the pediatric powder for oral solution.

Serious and Potentially Serious Adverse Reactions

To assure safe and effective use of moxifloxacin hydrochloride, patients should be informed of the following serious adverse reactions that have been associated with moxifloxacin hydrochloride and other fluoroquinolone use:

- Tendon Disorders: Patients should contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue moxifloxacin hydrochloride treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- Exacerbation of Myasthenia Gravis: Fluoroquinolones like moxifloxacin hydrochloride may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.
- Prolongation of the QT interval: Moxifloxacin hydrochloride may produce changes in the electrocardiogram (QTc interval prolongation). Moxifloxacin hydrochloride should be avoided in patients receiving Class IA (for example quinidine, procainamide) or Class III (for example amiodarone, sotalol) antiarrhythmic agents. Moxifloxacin hydrochloride may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants. The patients should inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, and acute myocardial ischemia. Patients should contact their physician if they experience

palpitations or fainting spells while taking moxifloxacin hydrochloride.

- Hypersensitivity Reactions: Patients should be advised that moxifloxacin hydrochloride may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose. Patients should discontinue moxifloxacin hydrochloride at the first sign of a skin rash or other signs of an allergic reaction.
- Convulsions: Convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking moxifloxacin hydrochloride if there is a history of this condition. Patients should also inform their physician if they are taking NSAIDs concurrently with moxifloxacin hydrochloride.
- Neurologic Adverse Effects (for example, dizziness, lightheadedness): moxifloxacin hydrochloride may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- Peripheral Neuropathies: If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should discontinue moxifloxacin hydrochloride and contact their physician.
- Photosensitivity/Phototoxicity: Patients should be informed that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.
- Diarrhea: Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids, Sucralfate, Multivitamins and other products containing Multivalent Cations

Quinolones form chelates with alkaline earth and transition metal cations. Oral administration of quinolones with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as didanosine chewable/buffered tablets or the pediatric powder for oral

solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin hydrochloride should be taken at least 4 hours before or 8 hours after these agents (see **Posology and method of administration** and **PHARMACOLOGICAL PROPERTIES**).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Although not observed with moxifloxacin hydrochloride in reported preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions (see **Special warnings and precautions for use**).

Drugs that Prolong QT

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin hydrochloride and other drugs that prolong the QTc interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of intravenous (IV) moxifloxacin hydrochloride in dogs. Therefore, moxifloxacin hydrochloride should be avoided with Class IA and Class III antiarrhythmics (see **Special warnings and precautions for use**).

An additive effect on QT interval prolongation of moxifloxacin hydrochloride and the following drugs cannot be excluded: antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide) or antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressive agents, certain antimicrobials (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine), certain antihistaminics (terfenadine, astemizole, mizolastine), others (cisapride, vincamine IV, bepridil, diphemanil). This effect might lead to an increased risk of ventricular arrhythmias, notably torsade de pointes. Therefore moxifloxacin hydrochloride is contraindicated in patients treated with these drugs (see **Contraindications**).

- ***Warfarin***

Quinolones, including moxifloxacin hydrochloride, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives (see **Undesirable effects** and **PHARMACOLOGICAL PROPERTIES**).

- ***Changes in INR***

A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibiotics, 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 antibiotic therapy cause the INR disorder. A precautionary measure would be to

more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate. Even if during an interaction study performed in healthy volunteers between moxifloxacin hydrochloride and warfarin, negative results have been observed, the precautionary measures as above stated should apply to warfarin as for other anticoagulants.

- ***Charcoal***

Concomitant administration of charcoal with an oral dose of 400 mg moxifloxacin hydrochloride leads to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases) [see **Overdose**].

- ***Digoxin***

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

- ***Glibenclamide***

In reported studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin hydrochloride with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of glibenclamide. The combination of glibenclamide and moxifloxacin hydrochloride 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 hydrochloride and glibenclamide.

- ***Others***

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

Interaction with Food

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

4.6 Pregnancy and lactation

Pregnancy

The use of moxifloxacin hydrochloride during pregnancy is contraindicated. The safety of moxifloxacin hydrochloride in human pregnancy has not been evaluated. Reversible joint injuries are described in children receiving some quinolones, 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.

Lactation

The use of moxifloxacin hydrochloride during breast feeding is contraindicated. As with other quinolones, moxifloxacin hydrochloride has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical data indicate that moxifloxacin hydrochloride passes into milk.

4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin hydrochloride on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin hydrochloride 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 **Undesirable effects**) or acute and short lasting loss of consciousness (syncope, see **Undesirable effects**). Patients should be advised to see how they react to moxifloxacin hydrochloride before driving or operating machinery.

4.8 Undesirable effects

Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse reactions are discussed in greater detail in the warnings and precautions section of the label:

- Tendinopathy and Tendon Rupture (see **Special warnings and precautions for use**) = QT Prolongation (see **Special warnings and precautions for use**)
- Hypersensitivity Reactions (see **Special warnings and precautions for use**)
- Other Serious and Sometimes Fatal Reactions (see **Special warnings and precautions for use**)
- Central Nervous System Effects (see **Special warnings and precautions for use**)
- *Clostridium difficile*-Associated Diarrhea (see **Special warnings and precautions for use**)
- Peripheral Neuropathy (see **Special warnings and precautions for use**) Photosensitivity/Phototoxicity (see **Special warnings and precautions for use**)
- Development of Drug Resistant Bacteria (see **Special warnings and precautions for use**)

Clinical Trial Experience

Because reported clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflects exposure to moxifloxacin hydrochloride reported in 14981 patients in 71 active controlled Phase II- IV clinical trials in different indications (see **Therapeutic indications**). The population studied had a mean age of 50 years (approximately 73% of the

population was <65 years of age), 50% were male, 63% were Caucasian, 12% were Asian and 9% were Black. Patients received moxifloxacin hydrochloride 400 mg once daily PO, IV, or sequentially (IV followed by PO). Treatment duration was usually 6-10 days, and the mean number of days on therapy was 9 days.

Discontinuation of moxifloxacin hydrochloride due to adverse events occurred in 5.0% of patients overall, 4.1% of patients treated with 400 mg PO, 3.9% with 400 mg IV and 8.2% with sequential therapy 400 mg PO/IV. The most common adverse events leading to discontinuation with the 400 mg PO doses were nausea (0.8%), diarrhea (0.5%), dizziness (0.5%), and vomiting (0.4%). The most common adverse event leading to discontinuation with the 400 mg IV dose was rash (0.5%). The most common adverse events leading to discontinuation with the 400 mg IV/PO sequential dose were diarrhea (0.5%), pyrexia (0.4%).

Adverse reactions occurring in ≥1% of moxifloxacin hydrochloride -treated patients and less common adverse reactions, occurring in 0.1 to <1% of moxifloxacin hydrochloride -treated patients, are shown in tables below. The most common adverse drug reactions (≥3%) are nausea, diarrhea, headache, and dizziness.

Table: Common (≥ 1.0%) Adverse Reactions Reported in Active-Controlled Clinical Trials with Moxifloxacin hydrochloride

System Organ Class	Adverse Reactions [a]	% (N=14,981)
Blood and Lymphatic System Disorders	Anemia	1.1
Gastrointestinal Disorders	Nausea Diarrhea Vomiting Constipation Abdominal pain Abdominal pain upper Dyspepsia	6.9 6.0 2.4 1.9 1.5 1.1 1.0
General disorders and administration site conditions	Pyrexia	1.1
Investigations	Alanine aminotransferase increased	1.1
Metabolism and Nutritional Disorder	Hypokalemia	1
Nervous System Disorders	Headache Dizziness	4.2 3.0
Psychiatric Disorders	Insomnia	1.9

[a]MedDRA Version 12.0

Table: Less Common (0.1 to <1.0%) Adverse Reactions Reported in Active- Controlled Clinical Trials with Moxifloxacin hydrochloride (N=14,981)

System Organ Class	Adverse Reactions[a]

Blood and Lymphatic System Disorders	Thrombocythaemia Eosinophilia Neutropenia Thrombocytopenia Leukopenia Leukocytosis
Cardiac Disorders	Atrial fibrillation Palpitations
	Tachycardia Cardiac failure congestive Angina pectoris Cardiac failure Cardiac arrest Bradycardia
Ear and Labyrinth Disorders	Vertigo Tinnitus
Eye Disorders	Vision blurred
Gastrointestinal Disorders	Dry mouth Abdominal discomfort Flatulence Abdominal distention Gastritis Gastroesophageal reflux disease
General Disorders and Administration Site Conditions	Fatigue Chest pain Asthenia Edema peripheral Pain Malaise Infusion site extravasation Edema Chills Chest discomfort Facial pain
Hepatobiliary	Hepatic function abnormal
Infections and Infestations	Vulvovaginal candidiasis Oral candidiasis Vulvovaginal mycotic infection Candidiasis Vaginal infection Oral fungal infection Fungal infection Gastroenteritis

Investigations	Aspartate aminotransferase increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Hepatic enzyme increased Electrocardiogram QT prolonged Blood lactate dehydrogenase increased Platelet count increased Blood amylase increased Blood glucose increased Lipase increased Hemoglobin decreased Blood creatinine increased Transaminases increased White blood cell count increased Blood urea increased Liver function test abnormal Hematocrit decreased Prothrombin time prolonged/ INR increased Eosinophil count increased Activated partial thromboplastin time prolonged Blood bilirubin increased Blood triglycerides increased Blood uric acid increased Blood pressure increased
Metabolism and Nutrition Disorders	Hyperglycemia Anorexia Hypoglycemia Hyperlipidemia Decreased appetite Dehydration
Musculoskeletal and Connective Tissue Disorders	Back pain Pain in extremity Arthralgia Myalgia Muscle spasms Musculoskeletal chest pain Musculoskeletal pain
Nervous System Disorders	Dysgeusia Somnolence Tremor Lethargy Paresthesia Tension headache Syncope

Psychiatric Disorders	Anxiety Confusional state Agitation Depression Nervousness Restlessness Hallucination Disorientation
Renal and Urinary Disorders	Renal failure Dysuria Renal failure acute
Reproductive System and Breast Disorders	Vulvovaginal pruritus
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea Asthma Wheezing Bronchospasm
Skin and Subcutaneous Tissue Disorders	Rash Pruritus Hyperhidrosis Erythema Urticaria Dermatitis allergic Night sweats
Vascular disorders	Hypertension Hypotension Phlebitis

[a]MedDRA Version 12.0

Laboratory Changes

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in ≥ 2% of patients and at an incidence greater than in controls included: increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin, bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose, pO_2, bilirubin, and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

Postmarketing Experience

Table below lists adverse reactions that have been identified during post-approval use of moxifloxacin hydrochloride. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table: Postmarketing Reports of Adverse Drug Reactions

System/ Organ Class	Adverse Reaction

Blood and Lymphatic System Disorders	Agranulocytosis Pancytopenia (see **Special warnings and precautions for use**)
Cardiac Disorders	Ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions)
Hepatobiliary Disorders	Hepatitis (predominantly cholestatic) Hepatic failure (including fatal cases) Jaundice Acute hepatic necrosis (see **Special warnings and precautions for use**)
Immune System Disorders	Anaphylactic reaction Anaphylactic shock Angioedema (including laryngeal edema) (see **Special warnings and precautions for use**)
Musculoskeletal and Connective Tissue Disorders	Tendon rupture (see **Special warnings and precautions for use**)
Nervous System Disorders	Altered coordination Abnormal gait Myasthenia gravis (see **Special warnings and precautions for use**)
Psychiatric Disorders	Psychotic reaction (very rarely culminating in self-endangering behavior)
Renal and Urinary Disorders	Renal dysfunction Interstitial nephritis (see **Special warnings and precautions for use**)
Respiratory, Thoracic and Mediastinal Disorders	Allergic pneumonitis (see **Special warnings and precautions for use**)
Skin and Subcutaneous Tissue Disorders	Photosensitivity/phototoxicity reaction Stevens-Johnson syndrome Toxic epidermal necrolysis (see **Special warnings and precautions for use**)

Other reported undesirable effects with moxifloxacin hydrochloride are fulminant hepatitis, hyperuricemia, increased prothrombin level, decreased INR, psychomotor hyperactivity, emotional lability, depersonalization, dysaesthesia, hyperaesthesia, ageusia, anosmia, abnormal dreams, seizures including grandmal convulsions, disturbed attention, speech disorders, amnesia, diplopia, transient loss of vision, deafness, unspecified arrhythmias, QT prolongation with hypokalemia, vasodilation, anorexia, dysphagia, stomatitis, increased, dry skin, exacerbation of symptoms of myasthenia gravis, muscle twitching, muscle weakness, pelvic pain, arthritis, muscle rigidity, sweating and antibiotic associated colitis.

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 hydrochloride: hypernatraemia, hypercalcaemia, haemolytic anemia, rhabdomyolysis,

photosensitivity reactions, peripheral neuropathy.

4.9 Overdose

Single oral overdoses up to 2.8 g were not associated with any serious adverse events. In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. ECG monitoring is recommended due to the possibility of QT interval prolongation. The patient should be carefully observed and given supportive treatment. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin hydrochloride exposure. About 3% and 9% of the dose of moxifloxacin hydrochloride, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and hemodialysis, respectively.

Single oral moxifloxacin hydrochloride doses of 2000, 500, and 1500 mg/kg were lethal to rats, mice, and cynomolgus monkeys, respectively. The minimum lethal intravenous dose in mice and rats was 100 mg/kg. Adverse clinical signs included CNS and gastrointestinal effects such as decreased activity, somnolence, tremor, convulsions, vomiting and diarrhea.

5. PHARMACOLOGICAL PROPERTIES [1, 2]

5.1 Pharmacodynamic properties

- *Mechanism of Action*

Moxifloxacin hydrochloride has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms. 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 C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

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

- *Drug Resistance*

In vitro resistance to moxifloxacin hydrochloride develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $< 1 \times 10^{-11}$ for Gram-positive bacteria.

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

- *Activity in vitro and in vivo*

Moxifloxacin hydrochloride has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **Therapeutic indications** section**.**

Aerobic Gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible) *Staphylococcus aureus* (methicillin- susceptible strains only) *Streptococcus anginosus*

Streptococcus constellatus

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]*)

Streptococcus pyogenes

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin- resistant *S. pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (MIC 2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic Gram-negative microorganisms

Enterobacter cloacae Escherichia coli
Haemophilus influenzae Haemophilus
parainfluenzae Klebsiella pneumoniae
Moraxella catarrhalis Proteus mirabilis

Anaerobic microorganisms

Bacteroides fragilis Bacteroides
thetaiotaomicron Clostridium perfringens
Peptostreptococcus species

Other microorganisms

Chlamydia pneumoniae Mycoplasma
pneumonia

The following *in vitro* data are available, **but their clinical significance is unknown.** Moxifloxacin hydrochloride exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 mcg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of moxifloxacin hydrochloride in treating clinical infections due to these microorganisms have not been established in adequate and well- controlled clinical trials.

Aerobic Gram-positive Microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains only)

Streptococcus agalactiae Streptococcus
viridans group

Aerobic Gram-negative Microorganisms

Citrobacter freundii Klebsiella

oxytoca Legionella pneumophila

Anaerobic Microorganisms

Fusobacterium species

Prevotella species

5.2 Pharmacokinetic properties

Absorption

Moxifloxacin hydrochloride, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin hydrochloride is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin hydrochloride.

Consumption of 1 cup of yogurt with moxifloxacin hydrochloride does not significantly affect the extent or rate of systemic absorption (AUC).

Table: The Mean (± SD) C_{max} and AUC Values Following Single and Multiple Doses of 400 mg Moxifloxacin hydrochloride Given Orally

	C_{max} (mg/L)	**AUC (mg h/L)**	**Half life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6[a]
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ± 1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

[a] Range of means from different studies

Table: The Mean (± SD) C_{max} and AUC Values Following Single and Multiple Doses of 400 mg Moxifloxacin hydrochloride given by 1 Hour I.V. Infusion

	C_{max} (mg/L)	**AUC (mg h/L)**	**Half-life (hr)**
Single Dose I.V.			
Healthy young male/female (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4[a]
Patients (n = 118)			
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		

≥ 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n = 12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients [b] (n = 107)			
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
≥ 65 years (n = 55)	4.7 ± 2.7		

[a] Range of means from different studies

[b] Expected C_{max} (concentration obtained around the time of the end of the infusion)

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

Moxifloxacin hydrochloride is approximately 30-50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin hydrochloride ranges from 1.7 to 2.7 L/kg. Moxifloxacin hydrochloride is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin hydrochloride has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral or intravenous administration of 400 mg. Moxifloxacin hydrochloride concentrations measured post-dose in various tissues and fluids following a 400 mg oral or IV dose are summarized in table below. The rates of elimination of moxifloxacin hydrochloride from tissues generally parallel the elimination from plasma.

Table: Moxifloxacin hydrochloride Concentrations (Mean ± SD) in Plasma and Tissues After a Single 400 mg Oral or Intravenous Dose[a]

Tissue or Fluid	**N**	**Plasma Concentration (µg/mL)**	**Tissue or Fluid Concentration (µg/mL or µg/g)**	**Tissue Plasma Ratio:**
Respiratory				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial Mucosa	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial Lining Fluid	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				

Maxillary Sinus Mucosa	4	3.7 ± 1.1[b]	7.6 ± 1.7	2.0 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1[b]	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1[b]	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal				
Blister Fluid	5	3.0 ± 0.5[c]	2.6 ± 0.9	0.9 ± 0.2
Subcutaneous Tissue	6	2.3 ± 0.4[d]	0.9 ± 0.3[e]	0.4 ± 0.6
Skeletal Muscle	6	2.3 ± 0.4[d]	0.9 ± 0.2[e]	0.4 ± 0.1
Intra-Abdominal				
Abdominal tissue	8	2.9 ± 0.5	7.6 ± 2.0	2.7 ± 0.8
Abdominal exudate	10	2.3 ± 0.5	3.5 ± 1.2	1.6 ± 0.7
Abscess fluid	6	2.7± 0.7	2.3 ± 1.5	0.8 ± 0.4

[a] all moxifloxacin hydrochloride concentrations were measured 3 hours after a single 400 mg dose, except the abdominal tissue and exudates concentrations which were measured at 2 hours post-dose and the sinus concentrations which were measured 3 hours post-dose after 5 days of dosing.

[b] N = 5

[c] N = 7

[d] N = 12

[e] Reflects only non-protein bound concentrations of drug.

Metabolism

Approximately 52% of an oral dose of moxifloxacin hydrochloride is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin hydrochloride metabolism, and is not affected by moxifloxacin hydrochloride. The sulfate conjugates (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces.

Approximately 14% of an oral dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin hydrochloride.

In vitro studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin hydrochloride does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin hydrochloride is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin hydrochloride is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted

as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/hr and 2.6 ± 0.5 L/hr, respectively.

Pharmacokinetics in Special Populations

- **Geriatric**

Following oral administration of 400 mg moxifloxacin hydrochloride for 10 days in 16 elderly (8 male; 8 female) and 17 young (8 male; 9 female) healthy volunteers, no age-related changes were observed in moxifloxacin hydrochloride pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin hydrochloride, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half- life was unchanged. No dosage adjustment is necessary based on age. In reported large phase III studies, the concentrations around the time of the end of the infusion in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients.

- **Pediatric**

The pharmacokinetics of moxifloxacin hydrochloride in pediatric subjects has not been studied.

- **Gender**

Following oral administration of 400 mg moxifloxacin hydrochloride daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were reported to be 8% and 16% higher, respectively, in females compared to males. There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration. A 400 mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin hydrochloride pharmacokinetics in this reported study (9 young females and 9 young males) showed no differences in AUC or C_{max} due to gender. Dosage adjustments based on gender are not necessary.

- **Race**

Steady-state moxifloxacin hydrochloride pharmacokinetics in male Japanese subjects were observed to be similar to those determined in Caucasians, with a mean C_{max} of 4.1 μg/mL, an AUC_{24} of 47 μg h/mL, and an elimination half-life of 14 hours, following 400 mg p.o. daily.

- **Renal Insufficiency**

The pharmacokinetic parameters of moxifloxacin hydrochloride are not significantly altered in mild, moderate, severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

In a reported single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin hydrochloride were reduced by 21% and 28% in the patients with moderate ($CL_{CR} \geq$ 30 and 60 mL/min) and severe (CL_{CR} < 30 mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the

mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8- fold) and 1.4-fold (ranging up to 2.5-fold), respectively.

The pharmacokinetics of single dose and multiple dose moxifloxacin hydrochloride is studied in patients with CL_{CR} < 20 mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin hydrochloride in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of moxifloxacin hydrochloride were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3, compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin hydrochloride are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal disease including those undergoing HD and CAPD has not been studied. Oral administration of 400 mg QD moxifloxacin hydrochloride for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{SS}) to moxifloxacin hydrochloride similar to that generally seen in healthy volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Both HD and CAPD removed only small amounts of moxifloxacin hydrochloride from the body approximately 9% by HD, and 3% by CAPD). HD and CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

- **Hepatic Insufficiency**

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 hydrochloride in patients with impaired liver function.

- **Photosensitivity Potential**

A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32 healthy volunteers (8 per group) demonstrated that moxifloxacin hydrochloride does not show phototoxicity in comparison to placebo. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin hydrochloride (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of moxifloxacin hydrochloride were not significantly different from placebo, while lomefloxacin significantly lowered the MED.

It is difficult to ascribe relative photosensitivity/phototoxicity among various fluoroquinolones during actual patient use because other factors play a role in determining a subject's susceptibility to this adverse event such as: a patient's skin pigmentation, frequency and duration of sun and artificial

ultraviolet light (UV) exposure, wearing of sunscreen and protective clothing, the use of other concomitant drugs and the dosage and duration of fluoroquinolone therapy (see **Special warnings and precautions for use**).

- **Drug-Drug Interactions**

The following drug interactions were studied in healthy volunteers or patients.

Antacids and iron significantly reduced bioavailability of moxifloxacin hydrochloride, as observed with other quinolones (see **Interaction with other medicinal products and other forms of interactions**).

Calcium, digoxin, itraconazole, morphine, probenecid, ranitidine, theophylline, and warfarin did not significantly affect the pharmacokinetics of moxifloxacin hydrochloride. These results and the data from *in vitro* studies suggest that moxifloxacin hydrochloride is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 enzymes.

Moxifloxacin hydrochloride had no clinically significant effect on the pharmacokinetics of atenolol, digoxin, glyburide, itraconazole, oral contraceptives, theophylline, and warfarin (see **Interaction with medicinal products and other forms of interactions**).

Antacids

When moxifloxacin hydrochloride (single 400 mg tablet dose) was administered two hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin hydrochloride, respectively. Moxifloxacin hydrochloride should be taken at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or didanosine chewable/ buffered tablets or the pediatric powder for oral solution (see **Posology and method of administration** and **Interaction with medicinal products and other forms of interactions**).

Atenolol

In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that observed when atenolol was given concomitantly with a single 400 mg oral dose of moxifloxacin hydrochloride. The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with a single dose of moxifloxacin hydrochloride

Calcium

Twelve healthy volunteers were administered concomitant moxifloxacin hydrochloride (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional two doses of calcium 12 and 24 hours after moxifloxacin hydrochloride administration. Calcium had no significant effect on the mean AUC of moxifloxacin hydrochloride. The mean C_{max} was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin

hydrochloride was given with calcium compared to when moxifloxacin hydrochloride was given alone (2.5 hours versus 0.9 hours). These differences are not considered to be clinically significant.

Digoxin

No significant effect of moxifloxacin hydrochloride (400 mg once daily for two days) on digoxin (0.6 mg as a single dose) AUC was observed in a reported study involving 12 healthy volunteers. The mean digoxin C_{max} increased by about 50% during the distribution phase of digoxin. This transient increase in digoxin C_{max} is not viewed to be clinically significant. Moxifloxacin hydrochloride pharmacokinetics was similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin hydrochloride or digoxin is required when these drugs are administered concomitantly.

Glyburide

In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment and for five days concurrently) mean AUC and C_{max} were 12% and 21% lower, respectively, when taken with moxifloxacin hydrochloride (400 mg once daily for five days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin hydrochloride in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin hydrochloride on the activity of glyburide. These interaction results are not viewed as clinically significant.

Iron

When moxifloxacin hydrochloride tablets were administered concomitantly with iron (ferrous sulfate 100 mg once daily for two days), the mean AUC and C_{max} of moxifloxacin was reduced by 39% and 59%, respectively. Moxifloxacin hydrochloride should only be taken more than 4 hours before or 8 hours after iron products (see **Posology and method of administration** and **Interaction with medicinal products and other forms of interactions**).

Itraconazole

In a study involving 11 healthy volunteers, there was no significant effect of itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the pharmacokinetics of moxifloxacin hydrochloride (a single 400 mg dose given on the 7th day of itraconazole dosing). In addition, moxifloxacin hydrochloride was shown not to affect the pharmacokinetics of itraconazole.

Morphine

No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the mean AUC and C_{max} of moxifloxacin hydrochloride (400 mg single dose) was observed in a reported study of 20 healthy male and female volunteers.

Oral Contraceptives

A placebo-controlled study in 29 healthy female subjects showed that moxifloxacin hydrochloride 400 mg daily for 7 days did not interfere with the hormonal suppression of oral contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered contraceptive agents.

Probenecid

Probenecid (500 mg twice daily for two days) did not alter the renal clearance and total amount of moxifloxacin hydrochloride (400 mg single dose) excreted renally in a study of 12 healthy volunteers.

Ranitidine

No significant effect of ranitidine (150 mg twice daily for three days as pretreatment) on the pharmacokinetics of moxifloxacin hydrochloride (400 mg single dose) was detected in a study involving 10 healthy volunteers.

Theophylline

No significant effect of moxifloxacin hydrochloride (200 mg every twelve hours for 3 days) on the pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the pharmacokinetics of moxifloxacin hydrochloride. The effect of co- administration of a 400 mg dose of moxifloxacin hydrochloride with theophylline has not been studied, but it is not expected to be clinically significant based on *in vitro* metabolic data showing that moxifloxacin hydrochloride does not inhibit the CYP1A2 isoenzyme.

Warfarin

No significant effect of moxifloxacin hydrochloride (400 mg once daily for eight days) on the pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day) was detected in a study involving 24 healthy volunteers. No significant change in prothrombin time was observed (see **Undesirable effects** and **Interaction with medicinal products and other forms of interactions**).

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to determine the carcinogenic potential of moxifloxacin hydrochloride have not been performed.

Moxifloxacin hydrochloride was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin hydrochloride in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin hydrochloride was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin hydrochloride was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys CNS toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin

hydrochloride or after prolonged treatment.

Moxifloxacin hydrochloride, like other quinolones, was genotoxic in *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 hydrochloride doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin hydrochloride was non-carcinogenic in an initiation-promotion study in rats.

Many quinolones are photoreactive and can induce phototoxic, photomutagenic and photocarcinogenic effects. In contrast, moxifloxacin hydrochloride was proven to be devoid of phototoxic and photogenotoxic properties when tested in a comprehensive programme of *in vitro* and *in vivo* studies. Under the same conditions other quinolones induced effects.

At high concentrations, moxifloxacin hydrochloride is an inhibitor of the rapid component 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 50fold the human dose (> 300 mg/kg), leading to plasma concentrations of 200 mg/l (more than 40fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

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

Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. 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.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin hydrochloride 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 hydrochloride. 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. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Lactose anhydrous, Povidone, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry Brown 03B86891 (which contains Hydroxy Propyl Methyl Cellulose, Titanium Dioxide, Polyethylene Glycol, Red Iron Oxide).

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Do not store above 30ºC. Protect from light and moisture.

6.5 Nature and contents of container

Moxifloxacin Tablets 400 mg are available in container packs of 30's and 500's.

Moxifloxacin Tablets 400 mg are available in Alu-PVC/PVDC blister pack:

- Each blister pack contains 5 tablets. 3 blister packs per carton (3x5's)
- Each blister pack contains 7 tablets. 5 blister packs per carton (5x7's)
- Each blister pack contains 10 tablets. 3 or 10 blister packs per carton (3x10's or 10x10's)

30's count container packs are configured with White opaque 40cc HDPE containers utilizing White opaque polypropylene 33 mm CR closure with wad having induction sealing liner.

500's count container packs are configured with White opaque 950cc HDPE containers utilizing White opaque polypropylene fine ribbed 53 mm CT screw cap poly-propylene closure.

Blister packs are sealed with Clear PVC/PVDC film on one side and Aluminum foil on the other side in the form of a PVC/PVDC-Alu Blister pack.

6.6 Instructions for use and handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MSN Laboratories Private Limited
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Sanath Nagar Industrial Estate, Sanath Nagar,
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8. DATE OF REVISION OF THE TEXT

October 2018

REFERENCES

1. Prescribing information for ***AVELOX®***, manufactured by Bayer HealthCare Pharmaceuticals

Inc. USA and distributed by Schering Corporation, USA, approved by FDA in August 2011, accessed online from http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=50084 on 22nd September 2011.

2. UK Summary of Product Characteristics of ***AVELOX*** 400 mg film-coated tablets, Bayer plc, UK, revised on 25th October 2010.

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