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Megaxin® IV

Solution for infusion

Moxifloxacin hydrochloride 400mg/250ml

Megaxin® Tablets

Film coated tablets

Moxifloxacin (as hydrochloride) 400mg

WARNING: TENDON EFFECTS and MYASTHENIA GRAVIS

Fluoroquinolones, including Megaxin IV / Megaxin Tablets, 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 [see *Warnings and Precautions (5.1)*].

Fluoroquinolones, including Megaxin IV / Megaxin Tablets, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Megaxin IV / Megaxin Tablets in patients with known history of myasthenia gravis [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

Megaxin IV is indicated for the treatment of adults (≥18 years of age) with

Community -Acquired Pneumonia caused by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, or Chlamydia pneumoniae and Complicated Skin and Skin Structure Infections caused by methicillin susceptible Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, or Enterobacter cloacae (See *CLINICAL STUDIES(14)*).

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. Therapy with Megaxin IV may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Megaxin Tablets is indicated for the treatment of the following bacterial infections in patients of 18 years and older

- Respiratory infections
- Uncomplicated Acute bacterial sinusitis (ABS)
- Acute exacerbations of chronic bronchitis (AECB)

Megaxin Tablets should be used to treat adequately diagnosed ABS and AECB 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 to resolve the infection.

- Community- acquired pneumonia, except severe cases.

Megaxin Tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection.

- Community-acquired spontaneous and wound infections of the skin and skin structure.

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. Therapy with Megaxin Tablets may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Patients

The dose of Megaxin 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 **Table 1**.

Table 1: 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 (SSSI)	400 mg	7
Complicated SSSI	400 mg	7-21

a)Due to the designated pathogens [see Indications and Usage (1), for IV use, see Use in Specific Populations (8.5)].

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 Megaxin IV may be switched to Megaxin Tablets when clinically indicated at the discretion of the physician.

2.2 Drug interactions with Multivalent Cations

Oral doses of Megaxin 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 [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.3)].

2.3 Administration Instructions

Megaxin film-coated Tablets

Megaxin Tablets can be taken with or without food; drink fluids liberally.

Megaxin IV Solution for Infusion

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Megaxin IV should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Megaxin IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. Caution: rapid or bolus intravenous infusion must be avoided.

Because only limited data are available on the compatibility of Megaxin IV with other intravenous substances, additives or other medications should not be added to Megaxin IV or infused simultaneously through the same intravenous line. If the same intravenous line or a Y-type line is used for sequential infusion of other drugs, or if the “piggyback” method of administration is used, the line should be flushed before and after infusion of Megaxin IV with an infusion solution compatible with Megaxin IV as well as with other drug(s) administered via this common line.

Megaxin IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1

0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Dextrose Injection, USP

Sterile Water for Injection, USP
10% Dextrose for Injection, USP
Lactated Ringer's for Injection

3 DOSAGE FORMS AND STRENGTHS

3.1 Megaxin Tablets

- Containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin)
- Oblong, dull red film-coated tablets
- Imprinted with BAYER on one side and M400 on the other

3.2 Megaxin IV

- Containing 400 mg moxifloxacin in 0.8% saline (moxifloxacin hydrochloride in sodium chloride injection) with pH ranging from 4.1 to 4.6.
- Ready-to-use 250 mL bottle for infusion. No further dilution is necessary
- Sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride

4 CONTRAINDICATIONS

Megaxin IV / Megaxin Tablets are contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including Megaxin IV / Megaxin Tablets, 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. Megaxin IV / Megaxin Tablets 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 Adverse Reactions (6.4)]*

5.2 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including Megaxin IV / Megaxin Tablets, 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 Megaxin IV / Megaxin Tablets in patients with known history of myasthenia gravis.

5.3 QT Prolongation

Megaxin IV / Megaxin Tablets has been shown to prolong the QT interval of the electrocardiogram in some patients. Following oral dosing with 400 mg of Megaxin IV / Megaxin Tablets, the mean (\pm SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 msec (\pm 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 (\pm 22) on Day 1 (n=667) and 7 msec (\pm 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 Megaxin IV / Megaxin Tablets and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of Megaxin IV / Megaxin Tablets and these drugs cannot be excluded; therefore caution should be exercised when Megaxin IV / Megaxin Tablets is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 Megaxin IV / Megaxin Tablets and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Megaxin IV / Megaxin Tablets should be used with caution in patients with ongoing proarrhythmic conditions, 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 Megaxin IV / Megaxin Tablets 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 Megaxin Tablets treated patients in a postmarketing observational study in which ECGs were not performed. Elderly patients using Megaxin IV may be more susceptible to drug-associated QT prolongation. [see *Use In Specific Populations*, (8.5).] In addition, Megaxin IV / Megaxin Tablets should be used with caution in patients with mild, moderate, or severe liver cirrhosis. [see *Clinical Pharmacology* (12.3)]

5.4 Hypersensitivity Reactions

Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including Megaxin IV / Megaxin Tablets. 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. Megaxin IV / Megaxin Tablets 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 *Adverse Reactions* (6)]

5.5 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 Megaxin IV / Megaxin Tablets. 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; leukopenia; 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 [see *Adverse Reactions* (6.4)].

5.6 Central Nervous System Effects

Fluoroquinolones, including Megaxin IV / Megaxin Tablets, may cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. [see *Adverse Reactions* (6.2, 6.4).]

Convulsions and increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones. Fluoroquinolones 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 Megaxin IV / Megaxin Tablets, the drug should be discontinued and appropriate measures instituted. As with all fluoroquinolones, Megaxin IV / Megaxin Tablets 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 *Drug Interactions* (7.4), *Adverse Reactions* (6.2, 6.4)]

5.7 Clostridium Difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Megaxin IV / Megaxin Tablets, 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 *Adverse Reactions* (6.2)].

5.8 Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones including Megaxin IV/Megaxin Tablets. Symptoms may occur soon after initiation of Megaxin IV/Megaxin Tablets and may be irreversible. Megaxin IV/Megaxin Tablets should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation [see *Adverse Reactions* (6.2, 6.4)].

5.9 Arthropathic Effects in Animals

The oral administration of Megaxin Tablets 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. [See *Animal Toxicology and/or Pharmacology* (13.2).]

5.10 Blood Glucose Disturbances

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Megaxin IV/Megaxin Tablets. In Megaxin IV/Megaxin Tablets -treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (for example, sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended [see Adverse Reactions (6.2)]. If a hypoglycemic reaction occurs, Megaxin IV/Megaxin Tablets should be discontinued and appropriate therapy should be initiated immediately. [See Adverse Reactions (6.2).]

5.11 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 Adverse Reactions (6.4) and Pharmacokinetics (12.3).]

5.12 Development of Drug Resistant Bacteria

Prescribing Megaxin IV / Megaxin Tablets 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.

5.13 Vision disorders

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

6 ADVERSE REACTIONS

6.1 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 leaflet:

- Tendinopathy and Tendon Rupture [see Warnings and Precautions (5.1)]
- QT Prolongation [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.4)]
- Other Serious and Sometimes Fatal Reactions [see Warnings and Precautions (5.5)]
- Central Nervous System Effects [see Warnings and Precautions (5.6)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.7)]
- Peripheral Neuropathy that may be irreversible [see Warnings and Precautions (5.8)]
- Blood Glucose Disturbances [see Warnings and Precautions (5.10)]
- Photosensitivity/Phototoxicity [see Warnings and Precautions (5.11)]
- Development of Drug Resistant Bacteria [see Warnings and Precautions (5.12)]

6.2 Clinical Trial Experience

Because 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 reflect exposure to Megaxin IV / Megaxin Tablets in 14,981 patients in 71 active controlled Phase II- IV clinical trials in different indications [see Indications and Usage (1)]. 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 Megaxin 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 Megaxin IV / Megaxin Tablets 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 $\geq 1\%$ of Megaxin IV / Megaxin Tablets -treated patients and less common adverse reactions, occurring in 0.1 to $<1\%$ of Megaxin IV / Megaxin Tablets -treated patients, are shown in **Table 2** and **Table 3**, respectively. The most common adverse drug reactions ($\geq 3\%$) are nausea, diarrhea, headache, and dizziness.

Table 2 Common ($\geq 1.0\%$) Adverse Reactions Reported in Active-Controlled Clinical Trials with Megaxin IV / Megaxin Tablets

System Organ Class	Adverse Reactions ^a	% (N=14,981)
Blood and Lymphatic System Disorders	Anemia	1.1
Gastrointestinal Disorders	Nausea	6.9
	Diarrhea	6.0
	Vomiting	2.4
	Constipation	1.9
	Abdominal pain	1.5
	Abdominal pain upper	1.1
	Dyspepsia	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	4.2
	Dizziness	3.0
Psychiatric Disorders	Insomnia	1.9

a) MedDRA Version 12.0

Table 3 Less Common (0.1 to $<1.0\%$) Adverse Reactions Reported in Active-Controlled Clinical Trials with Megaxin IV / Megaxin Tablets (N=14,981)

System Organ Class	Adverse Reactions ^a
Blood and Lymphatic System Disorders	Thrombocythemia Eosinophilia Neutropenia Thrombocytopenia Leukopenia Leukocytosis
Cardiac Disorders	Atrial fibrillation Palpitations Tachycardia Cardiac failure congestive Angina pectoris Cardiac failure Cardiac arrest Bradycardia

System Organ Class	Adverse Reactions^a
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 disorders	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 Eosinophil count increased Activated partial thromboplastin time prolonged Blood bilirubin increased Blood triglycerides increased Blood uric acid increased Blood pressure increased

System Organ Class	Adverse Reactions^a
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 Hypoesthesia 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

6.3 Laboratory Changes

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in $\geq 2\%$ 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, pO₂, 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.

6.4 Postmarketing Experience

Table 4 lists adverse reactions that have been identified during post-approval use of Megaxin IV / Megaxin Tablets. 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 4: Postmarketing Reports of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	Agranulocytosis Pancytopenia <i>[see Warnings and Precautions (5.5)]</i>
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)
Ear and Labyrinth Disorders	Hearing impairment, including deafness <u>(reversible in majority of cases)</u>
Eye Disorders	Vision loss (especially in the course of CNS reactions, transient in majority of cases)
Hepatobiliary Disorders	Hepatitis (predominantly cholestatic) Hepatic failure (including fatal cases) Jaundice Acute hepatic necrosis <i>[see Warnings and Precautions (5.5)]</i>
Immune System Disorders	Anaphylactic reaction Anaphylactic shock Angioedema (including laryngeal edema) <i>[see Warnings and Precautions (5.4, 5.5)]</i>
Musculoskeletal and Connective Tissue Disorders	Tendon rupture <i>[see Warnings and Precautions (5.1)]</i>
Nervous System Disorders	Altered coordination Abnormal gait <i>[see Warnings and Precautions (5.8)]</i> Myasthenia gravis (exacerbation of) <i>[see Warnings and Precautions (5.2)]</i> Muscle weakness Peripheral neuropathy, (that may be irreversible), polyneuropathy <i>[see Warnings and Precautions (5.8)]</i>
Psychiatric Disorders	Psychotic reaction (very rarely culminating in self-injurious behavior such as suicidal ideation/thoughts or suicide attempts <i>[see Warnings and Precautions (5.6)]</i>)
Renal and Urinary Disorders	Renal dysfunction

	Interstitial nephritis <i>[see Warnings and Precautions (5.5)]</i>
Respiratory, Thoracic and Mediastinal Disorders	Allergic pneumonitis <i>[see Warnings and Precautions (5.5)]</i>
Skin and Subcutaneous Tissue Disorders	Photosensitivity/phototoxicity reaction <i>[see Warnings and Precautions (5.11)]</i> Stevens-Johnson syndrome Toxic epidermal necrolysis <i>[see Warnings and Precautions (5.5)]</i>

7 DRUG INTERACTIONS

7.1 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, Megaxin IV / Megaxin Tablets should be taken at least 4 hours before or 8 hours after these agents. *[See Dosage and Administration (2.2), Pharmacokinetics (12.3)]*

7.2 Warfarin

Quinolones, including Megaxin IV / Megaxin Tablets, 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 Adverse Reactions (6.2, 6.3), Pharmacokinetics (12.3)]*.

7.3 Antidiabetic Agents

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with fluoroquinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered. If a hypoglycemic reaction occurs, Megaxin IV / Megaxin Tablets should be discontinued and appropriate therapy should be initiated immediately. *[See Warnings and Precautions (5.10); Adverse Reactions (6.2).]*

7.4 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Although not observed with Megaxin IV / Megaxin Tablets in 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 Warnings and Precautions (5.6)]*.

7.5 Drugs that Prolong QT

There is limited information available on the potential for a pharmacodynamic interaction in humans between Megaxin IV / Megaxin Tablets and other drugs that prolong the QTc interval of the electrocardiogram. Sotalolol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of intravenous (IV) Megaxin in dogs. Therefore, Megaxin IV / Megaxin Tablets should be avoided with Class IA and Class III antiarrhythmics. *[See Warnings and Precautions, (5.3), Nonclinical Toxicology (13.2)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Because no adequate or well-controlled studies have been conducted in pregnant women, Megaxin IV / Megaxin Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area (mg/m²)) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

8.3 Nursing Mothers

Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human milk. Because of the potential for serious adverse reactions in infants who are nursing from mothers taking Megaxin IV / Megaxin Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Megaxin IV / Megaxin Tablets causes arthropathy in juvenile animals [see *Boxed Warning, Warnings and Precautions (5.9)*, and *Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as Megaxin IV / Megaxin Tablets. 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 Megaxin IV / Megaxin Tablets to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue Megaxin IV / Megaxin Tablets and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur. [see *Boxed Warning, Warnings and Precautions (5.1)*, and *Adverse Reactions (6.4)*.]

In controlled multiple-dose clinical trials, 23% of patients receiving oral Megaxin 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 Megaxin in patients aged 65 or older compared to younger adults.

In trials of intravenous use, 42% of Megaxin IV / Megaxin Tablets 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 demonstrate that the safety of intravenous Megaxin 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, Megaxin IV / Megaxin Tablets 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 *Warnings and Precautions* (5.3), *Drug Interactions* (7.5), and *Clinical Pharmacology* (12.3).]

8.6 Renal Impairment

The pharmacokinetic parameters of moxifloxacin 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) [see *Dosage and Administration* (2), and *Clinical Pharmacology* (12.3).]

8.7 Hepatic Impairment

No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency (Child-Pugh Classes A, B, or C). However, due to metabolic disturbances associated with hepatic insufficiency, which may lead to QT prolongation, Megaxin IV / Megaxin Tablets should be used with caution in these patients [see *Warnings and Precaution* (5.3), and *Clinical Pharmacology*, (12.3)].

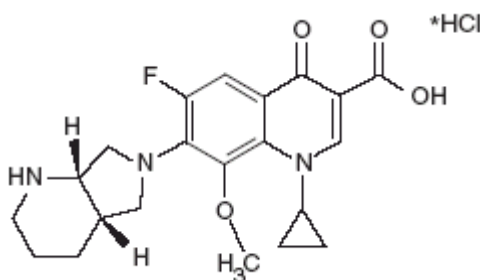
10 OVERDOSAGE

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 exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and hemodialysis, respectively.

Single oral Megaxin 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.

11 DESCRIPTION

Megaxin IV / Megaxin Tablets (moxifloxacin) hydrochloride is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is $C_{21}H_{24}FN_3O_4 \cdot HCl$ and its chemical structure is as follows:



11.1 Megaxin Tablets

- Megaxin Tablets are available as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin).
- The inactive ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, macrogol 4000 and ferric oxide red.

11.2 Megaxin IV

- Megaxin IV is available in glass bottle 250ml colorless glass type 2 for infusion containing 400mg of moxifloxacin. as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin) with pH ranging from 4.1 to 4.6.
- The appearance of the intravenous solution is yellow. The color does not affect, nor is it indicative of, product stability.
- The inactive ingredients are sodium chloride, Water for Injection, and may include hydrochloric acid 1N and/or sodium hydroxide solution 2N for pH adjustment.
- Megaxin IV contains approximately 34.2 mEq (787 mg) of sodium in 250 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Megaxin IV / Megaxin Tablets is a member of the fluoroquinolone class of antibacterial agents [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

Absorption

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a high fat meal (that is, 500 calories from fat) does not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

Table 5: Mean (\pm SD) C_{\max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally

	C_{\max} (mg/L)	AUC (mg·h/L)	Half-life (hr)
Single Dose Oral Healthy (n = 372)	3.1 ± 1	36.1 ± 9.1	$11.5 - 15.6^a$
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48 ± 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	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

a) Range of means from different studies

Table 6: Mean (\pm SD) C_{\max} and AUC values following single and multiple doses of 400 mg moxifloxacin given by 1 hour IV infusion

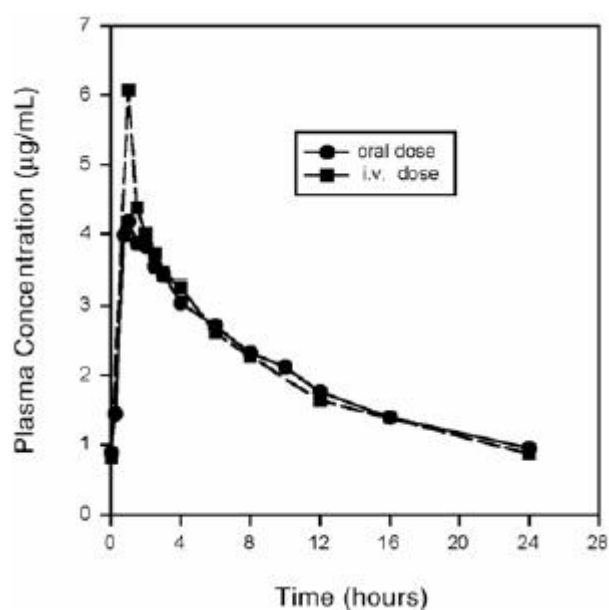
	C_{\max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose IV Healthy young male/female (n = 56)	3.9 \pm 0.9	39.3 \pm 8.6	8.2 - 15.4 ^a
Patients (n = 118)			
Male (n = 64)	4.4 \pm 3.7		
Female (n = 54)	4.5 \pm 2		
< 65 years (n = 58)	4.6 \pm 4.2		
\geq 65 years (n = 60)	4.3 \pm 1.3		
Multiple Dose IV			
Healthy young male (n = 8)	4.2 \pm 0.8	38 \pm 4.7	14.8 \pm 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 \pm 1.3	48.2 \pm 0.9	10.1 \pm 1.6
Patients ^b (n = 107)			
Male (n = 58)	4.2 \pm 2.6		
Female (n = 49)	4.6 \pm 1.5		
<65 years (n = 52)	4.1 \pm 1.4		
\geq 65 years (n = 55)	4.7 \pm 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 (\pm SD) elimination half-life from plasma is 12 \pm 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

**Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg
Either Orally (n=10) or by IV Infusion (n=12)**



Distribution

Moxifloxacin is approximately 30-50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, subcutaneous tissue, skeletal muscle, and abdominal tissues and fluids following oral or intravenous administration of 400 mg. Moxifloxacin concentrations measured post-dose in various tissues and fluids following a 400 mg oral or IV dose are summarized in **Table 7**. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Table 7: Moxifloxacin Concentrations (mean \pm SD) in Tissues and the Corresponding Plasma Concentrations After a Single 400 mg Oral or Intravenous Dose^a

Tissue or Fluid	N	Plasma Concentration (mcg/mL)	Tissue or Fluid Concentration (mcg/mL or mcg/g)	Tissue Plasma Ratio
Respiratory				
Alveolar Macrophages	5	3.3 \pm 0.7	61.8 \pm 27.3	21.2 \pm 10
Bronchial Mucosa	8	3.3 \pm 0.7	5.5 \pm 1.3	1.7 \pm 0.3
Epithelial Lining Fluid	5	3.3 \pm 0.7	24.4 \pm 14.7	8.7 \pm 6.1
Sinus				
Maxillary Sinus Mucosa	4	3.7 \pm 1.1 ^b	7.6 \pm 1.7	2 \pm 0.3
Anterior Ethmoid Mucosa	3	3.7 \pm 1.1 ^b	8.8 \pm 4.3	2.2 \pm 0.6
Nasal Polyps	4	3.7 \pm 1.1 ^b	9.8 \pm 4.5	2.6 \pm 0.6
Skin, Musculoskeletal				
Blister Fluid	5	3 \pm 0.5 ^c	2.6 \pm 0.9	0.9 \pm 0.2
Subcutaneous Tissue	6	2.3 \pm 0.4 ^d	0.9 \pm 0.3 ^e	0.4 \pm 0.6
Skeletal Muscle	6	2.3 \pm 0.4 ^d	0.9 \pm 0.2 ^e	0.4 \pm 0.1
Intra-Abdominal				
Abdominal tissue	8	2.9 \pm 0.5	7.6 \pm 2	2.7 \pm 0.8
Abdominal exudate	10	2.3 \pm 0.5	3.5 \pm 1.2	1.6 \pm 0.7
Abscess fluid	6	2.7 \pm 0.7	2.3 \pm 1.5	0.8 \pm 0.4

- a) All moxifloxacin concentrations were measured 3 hours after a single 400 mg dose, except the abdominal tissue and exudate 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 or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous 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.

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

Excretion

Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of $96\% \pm 4\%$ of an oral dose is excreted as either unchanged drug or known metabolites. The mean (\pm SD) apparent total body clearance and renal clearance are 12 ± 2 L/hr and 2.6 ± 0.5 L/hr, respectively.

Pharmacokinetics in Specific Populations

Geriatric

Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 17 young (8 male; 9 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin, 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 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. [see Use In Specific Populations (8.5).]

Pediatric

The pharmacokinetics of moxifloxacin in pediatric subjects has not been studied [see Use In Specific Populations (8.4)].

Gender

Following oral administration of 400 mg moxifloxacin 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 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 pharmacokinetics in this 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 pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean C_{\max} of 4.1 mcg/mL, an AUC₂₄ of 47 mcg•h/mL, and an elimination half-life of 14 hours, following 400 mg p.o. daily.

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin 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 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 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. [see Use in Specific Populations (8.6).]

The pharmacokinetics of single dose and multiple dose moxifloxacin were 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 in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{\max} values of moxifloxacin 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 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 Megaxin Tablets for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{ss}) to moxifloxacin 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 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

No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency (Child-Pugh Classes A, B, or C). However, due to metabolic disturbances associated with hepatic insufficiency, which may lead to QT prolongation, Megaxin IV/ Megaxin Tablets should be used with caution in these patients [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.7)].

In 400 mg single oral dose studies in 6 patients with mild (Child-Pugh Class A) and 10 patients with moderate (Child-Pugh Class B) hepatic insufficiency, moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls.

The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. In a subset of patients participating in a clinical trial, the plasma concentrations of moxifloxacin and metabolites determined approximately at the moxifloxacin T_{max} following the first intravenous or oral Megaxin dose in the Child-Pugh Class C patients (n=10) were similar to those in the Child-Pugh Class A/B patients (n=5), and also similar to those observed in healthy volunteer studies.

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 Megaxin IV / Megaxin Tablets does not show phototoxicity in comparison to placebo. The minimum erythematous dose (MED) was measured before and after treatment with Megaxin IV / Megaxin Tablets (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of Megaxin IV / Megaxin Tablets 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 *Warnings and Precautions* (5.11), *Adverse Reactions* (6.3)].

Drug-Drug Interactions

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

Antacids and iron significantly reduced bioavailability of moxifloxacin, as observed with other quinolones [see *Drug Interactions* (7.1)].

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

Moxifloxacin had no clinically significant effect on the pharmacokinetics of atenolol, digoxin, glyburide, itraconazole, oral contraceptives, theophylline, cyclosporine and warfarin [see *Drug Interactions (7.2)*].

Antacids

When moxifloxacin (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, respectively. Moxifloxacin 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 *Dosage and Administration (2.2)*, *Drug Interactions (7.1)*].

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. The mean C_{max} of single dose atenolol decreased by about 10% following co-administration with a single dose of moxifloxacin.

Calcium

Twelve healthy volunteers were administered concomitant moxifloxacin (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 administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin 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 (400 mg once daily for two days) on digoxin (0.6 mg as a single dose) AUC was detected in a 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 pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin 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 (400 mg once daily for five days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically significant.

Iron

When moxifloxacin 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 should only be taken more than 4 hours before or 8 hours after iron products. [see *Dosage and Administration (2.2)*, *Drug Interactions (7.1)*].

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 (a single 400 mg dose given on the 7th day of itraconazole dosing). In addition, moxifloxacin 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 (400 mg single dose) was observed in a study of 20 healthy male and female volunteers.

Oral Contraceptives

A placebo-controlled study in 29 healthy female subjects showed that moxifloxacin 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 (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 (400 mg single dose) was detected in a study involving 10 healthy volunteers.

Theophylline

No significant effect of moxifloxacin (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. The effect of co-administration of a 400 mg dose of moxifloxacin with theophylline has not been studied, but it is not expected to be clinically significant based on *in vitro* metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.

Warfarin

No significant effect of moxifloxacin (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 *Adverse Reactions (6.2)*, *Drug Interactions (7.2)*].

12.4 Microbiology

Mechanism of Action

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.

Mechanism of Resistance

The mechanism of action for fluoroquinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. Resistance to fluoroquinolones occurs primarily by a mutation in topoisomerase II (DNA gyrase) or topoisomerase IV genes, decreased outer membrane permeability or drug efflux. *In vitro* resistance to moxifloxacin 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

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

Moxifloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections . [see *Indications and Usage (1)*].

Gram-positive bacteria

- *Enterococcus faecalis*
- *Staphylococcus aureus*
- *Streptococcus anginosus*
- *Streptococcus constellatus*
- *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP] **)
- *Streptococcus pyogenes*

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

Gram-negative bacteria

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

Anaerobic bacteria

- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Clostridium perfringens*
- *Peptostreptococcus species*

Other microorganisms

- *Chlamydophila pneumoniae*
- *Mycoplasma pneumoniae*

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for moxifloxacin. However, the efficacy of Megaxin IV / Megaxin Tablets in treating clinical infections due to these bacteria **has not been** established in adequate and well controlled clinical trials.

Gram-positive bacteria

- *Staphylococcus epidermidis*
- *Streptococcus agalactiae*
- *Streptococcus viridans group*

Gram-negative bacteria

- *Citrobacter freundii*
- *Klebsiella oxytoca*
- *Legionella pneumophila*

Anaerobic bacteria

- *Fusobacterium species*
- *Prevotella species*

Susceptibility Tests Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community- acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

- **Dilution Techniques:**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and/or agar). The MIC values should be interpreted according to the criteria in **Table 8**.

- **Diffusion Techniques:**

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size prove should be determined using a standardized test method. This procedure uses paper disks impregnated with 5 mcg moxifloxacin to test the susceptibility of bacteria to moxifloxacin. The disc diffusion interpretive criteria are provided in **Table 8**.

- **Anaerobic Techniques:**

For anaerobic bacteria, the susceptibility to moxifloxacin can be determined by a standardized test method. The MIC values obtained should be interpreted according to the criteria provided in **Table 8**.

Table 8: Susceptibility Test Interpretive Criteria for Moxifloxacin

Species	MIC (mcg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥19	16–18	≤15
<i>Enterococcus faecalis</i>	≤1	2	≥4	≥18	15–17	≤14
<i>Staphylococcus aureus</i>	≤2	4	≥8	≥19	16–18	≤15
<i>Haemophilus influenzae</i>	≤1	a	a	≥18	a	a
<i>Haemophilus parainfluenzae</i>	≤1	a	a	≥18	a	a
<i>Streptococcus pneumoniae</i>	≤1	2	≥4	≥18	15–17	≤14
<i>Streptococcus species</i>	≤1	2	≥4	≥18	15–17	≤14
<i>Anaerobic bacteria</i>	≤2	4	≥8	-	-	-
S=susceptible, I=Intermediate, and R=resistant. ^a) The current absence of data on moxifloxacin-resistant isolates precludes defining any results other than “Susceptible”. Isolates yielding test results (MIC or zone diameter) other than susceptible, should be submitted to a reference laboratory for additional testing.						

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

- **Quality Control**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay and the techniques of the individuals performing the test. Standard moxifloxacin powder should provide the following range of MIC values noted in Table 9. For the diffusion technique using the 5 mcg moxifloxacin disk, the criteria in **Table 9** should be achieved.

Table 9: Acceptable Quality Control Ranges for Moxifloxacin

Strains	MIC range (mcg/mL)	Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.06–0.5	-
<i>Escherichia coli</i> ATCC 25922	0.008–0.06	28–35
<i>Haemophilus influenzae</i> ATCC 49247	0.008–0.03	31–39
<i>Staphylococcus aureus</i> ATCC 29213	0.015–0.06	-
<i>Staphylococcus aureus</i> ATCC 25923	-	28–35
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06–0.25	25–31
<i>Bacteroides fragilis</i> ATCC 25285	0.125–0.5	-
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	1–4	-
<i>Eubacterium lentum</i> ATCC 43055	0.125–0.5	-

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Moxifloxacin 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 in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin 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 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.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 12 times the maximum recommended human dose based on body surface area (mg/m²), or at intravenous doses as high as 45 mg/kg/day, approximately equal to the maximum recommended human dose based on body surface area (mg/m²). At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin \geq 30 mg/kg/day (approximately 1.5 times the maximum recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy. There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and 500 mg/kg/day, respectively.

Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (for example, seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen. Some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).

A QT-prolonging effect of moxifloxacin was found in dog studies, at plasma concentrations about five times the human therapeutic level. The combined infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation in dogs than that induced by the same dose (30 mg/kg) of moxifloxacin alone. Electrophysiological *in vitro* studies suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism.

No signs of local intolerance were observed in dogs when moxifloxacin was administered intravenously. After intra-arterial injection, inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of Megaxin IV should be avoided.

14 CLINICAL STUDIES

14.1 Acute Bacterial Exacerbation of Chronic Bronchitis

Megaxin Tablets (400 mg once daily for five days) were evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in a randomized, double-blind, controlled clinical trial conducted in the US. This study compared Megaxin IV / Megaxin Tablets with clarithromycin (500 mg twice daily for 10 days) and enrolled 629 patients. Clinical success was assessed at 7-17 days post-therapy. The clinical success for Megaxin IV / Megaxin Tablets was 89% (222/250) compared to 89% (224/251) for clarithromycin.

Table 10: Clinical Success Rates at Follow-Up Visit for Clinically Evaluable Patients by Pathogen (Acute Bacterial Exacerbation of Chronic Bronchitis)

PATHOGEN	Megaxin IV / Megaxin Tablets	Clarithromycin
<i>Streptococcus pneumoniae</i>	16/16 (100%)	20/23 (87%)
<i>Haemophilus influenzae</i>	33/37 (89%)	36/41 (88%)
<i>Haemophilus parainfluenzae</i>	16/16 (100%)	14/14 (100%)
<i>Moraxella catarrhalis</i>	29/34 (85%)	24/24 (100%)
<i>Staphylococcus aureus</i>	15/16 (94%)	6/8 (75%)
<i>Klebsiella pneumoniae</i>	18/20 (90%)	10/11 (91%)

The microbiological eradication rates (eradication plus presumed eradication) in Megaxin IV / Megaxin Tablets treated patients were *Streptococcus pneumoniae* 100%, *Haemophilus influenzae* 89%, *Haemophilus parainfluenzae* 100%, *Moraxella catarrhalis* 85%, *Staphylococcus aureus* 94%, and *Klebsiella pneumoniae* 85%.

14.2 Community -Acquired Pneumonia

A randomized, double-blind, controlled clinical trial was conducted in the US to compare the efficacy of Megaxin Tablets (400 mg once daily) to that of high-dose clarithromycin (500 mg twice daily) in the treatment of patients with clinically and radiologically documented community -acquired pneumonia. This study enrolled 474 patients (382 of whom were valid for the efficacy analysis conducted at the 14 - 35 day follow-up visit). Clinical success for clinically evaluable patients was 95% (184/194) for Megaxin IV / Megaxin Tablets and 95% (178/188) for high dose clarithromycin.

A randomized, double-blind, controlled trial was conducted in the US and Canada to compare the efficacy of sequential IV/PO Megaxin 400 mg QD for 7-14 days to an IV/PO fluoroquinolone control (trovafloxacin or levofloxacin) in the treatment of patients with clinically and radiologically documented community -acquired pneumonia. This study enrolled 516 patients, 362 of whom were valid for the efficacy analysis conducted at the 7-30 day post-therapy visit. The clinical success rate was 86% (157/182) for Megaxin IV / Megaxin Tablets therapy and 89% (161/180) for the fluoroquinolone comparators.

An open-label ex-US study that enrolled 628 patients compared Megaxin IV / Megaxin Tablets to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The intravenous formulations of the comparators are not FDA approved. The clinical success rate at Day 5-7 for Megaxin IV /

Megaxin Tablets therapy was 93% (241/258) and demonstrated superiority to amoxicillin/clavulanate ± clarithromycin (85%, 239/280) [95% C.I. of difference in success rates between moxifloxacin and comparator (2.9%, 13.2%)]. The clinical success rate at the 21-28 days post-therapy visit for Megaxin IV / Megaxin Tablets was 84% (216/258), which also demonstrated superiority to the comparators (74%, 208/280) [95% C.I. of difference in success rates between moxifloxacin and comparator (2.6%, 16.3%)]. The clinical success rates by pathogen across four CAP studies are presented in **Table11**.

Table 11: Clinical Success Rates By Pathogen (Pooled CAP Studies)

PATHOGEN	Megaxin IV / Megaxin Tablets	
<i>Streptococcus pneumoniae</i>	80/85	(94%)
<i>Staphylococcus aureus</i>	17/20	(85%)
<i>Klebsiella pneumoniae</i>	11/12	(92%)
<i>Haemophilus influenzae</i>	56/61	(92%)
<i>Chlamydophila pneumoniae</i>	119/128	(93%)
<i>Mycoplasma pneumoniae</i>	73/76	(96%)
<i>Moraxella catarrhalis</i>	11/12	(92%)

14.3 Community -Acquired Pneumonia caused by Multi-Drug Resistant *Streptococcus pneumoniae* (MDRSP)*

Megaxin IV / Megaxin Tablets was effective in the treatment of community- acquired pneumonia (CAP) caused by multi-drug resistant *Streptococcus pneumoniae* MDRSP* isolates. Of 37 microbiologically evaluable patients with MDRSP isolates, 35 patients (95%) achieved clinical and bacteriological success post-therapy. The clinical and bacteriological success rates based on the number of patients treated are shown in **Table12**.

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

Table 12: Clinical and Bacteriological Success Rates for Megaxin IV / Megaxin Tablets -Treated MDRSP CAP Patients (Population: Valid for Efficacy)

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N ^a	%	n/N ^b	%
Penicillin-resistant	21/21	100% ^c	21/21	100% ^c
2 nd generation cephalosporin-resistant	25/26	96% ^c	25/26	96% ^c
Macrolide-resistant ^d	22/23	96%	22/23	96%
Trimethoprim/sulfamethoxazole-resistant	28/30	93%	28/30	93%
Tetracycline-resistant	17/18	94%	17/18	94%

a) n = number of patients successfully treated; N = number of patients with MDRSP (from a total of 37 patients)

b) n = number of patients successfully treated (presumed eradication or eradication); N = number of patients with MDRSP (from a total of 37 patients)

c) One patient had a respiratory isolate that was resistant to penicillin and cefuroxime but a blood isolate that was intermediate to penicillin and cefuroxime. The patient is included in the database based on the respiratory isolate.

d) Azithromycin, clarithromycin, and erythromycin were the macrolide antimicrobials tested.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in **Table13**.

Table 13: Clinical Success Rates and Microbiological Eradication Rates for Resistant *Streptococcus pneumoniae* (Community- Acquired Pneumonia)

<i>S. pneumoniae</i> with MDRSP	Clinical Success	Bacteriological Eradication Rate
Resistant to 2 antimicrobials	12/13 (92.3 %)	12/13 (92.3 %)
Resistant to 3 antimicrobials	10/11 (90.9 %) ^a	10/11 (90.9 %) ^a
Resistant to 4 antimicrobials	6/6 (100%)	6/6 (100%)
Resistant to 5 antimicrobials	7/7 (100%) ^a	7/7 (100%) ^a
Bacteremia with MDRSP	9/9 (100%)	9/9 (100%)

a) One patient had a respiratory isolate resistant to 5 antimicrobials and a blood isolate resistant to 3 antimicrobials. The patient was included in the category resistant to 5 antimicrobials.

14.4 Acute Bacterial Sinusitis

In a controlled double-blind study conducted in the US, Megaxin Tablets (400 mg once daily for ten days) were compared with cefuroxime axetil (250 mg twice daily for ten days) for the treatment of acute bacterial sinusitis. The trial included 457 patients valid for the efficacy analysis. Clinical success (cure plus improvement) at the 7 to 21 day post-therapy test of cure visit was 90% for Megaxin IV/ Megaxin Tablets and 89% for cefuroxime.

An additional non-comparative study was conducted to gather bacteriological data and to evaluate microbiological eradication in adult patients treated with Megaxin IV/ Megaxin Tablets 400 mg once daily for seven days. All patients (n = 336) underwent antral puncture in this study. Clinical success rates and eradication/presumed eradication rates at the 21 to 37 day follow-up visit were 97% (29 out of 30) for *Streptococcus pneumoniae*, 83% (15 out of 18) for *Moraxella catarrhalis*, and 80% (24 out of 30) for *Haemophilus influenzae*.

14.5 Uncomplicated Skin and Skin Structure Infections

A randomized, double-blind, controlled clinical trial conducted in the US compared the efficacy of Megaxin IV / Megaxin Tablets 400 mg once daily for seven days with cephalexin HCl 500 mg three times daily for seven days. The percentage of patients treated for uncomplicated abscesses was 30%, furuncles 8%, cellulitis 16%, impetigo 20%, and other skin infections 26%. Adjunctive procedures (incision and drainage or debridement) were performed on 17% of the Megaxin IV / Megaxin Tablets treated patients and 14% of the comparator treated patients. Clinical success rates in evaluable patients were 89% (108/122) for Megaxin I V / Megaxin Tablets and 91% (110/121) for cephalexin HCl.

14.6 Complicated Skin and Skin Structure Infections

Two randomized, active controlled trials of cSSSI were performed. A double-blind trial was conducted primarily in North America to compare the efficacy of sequential IV/PO Megaxin 400 mg QD for 7-14 days to an IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients with cSSSI. This study enrolled 617 patients, 335 of which were valid for the efficacy analysis. A second open-label International study compared Megaxin IV / Megaxin Tablets 400 mg QD for 7-21 days to sequential IV/PO beta-lactam/beta-lactamase inhibitor control in the treatment of patients with cSSSI. This study enrolled 804 patients, 632 of which were valid for the efficacy analysis. Surgical incision and drainage or debridement was performed on 55% of the Megaxin IV / Megaxin Tablets treated and 53% of the comparator treated patients in these studies and formed an integral part of therapy for this indication. Success rates varied with the type of diagnosis ranging from 61% in patients with infected ulcers to 90% in patients with complicated erysipelas. These rates were similar to

those seen with comparator drugs. The overall success rates in the evaluable patients and the clinical success by pathogen are shown in **Tables 14 and 15**.

Table 14: Overall Clinical Success Rates in Patients with Complicated Skin and Skin Structure Infections

Study	Megaxin IV / Megaxin Tablets n/ N (%)	Comparator n/N (%)	95% Confidence Interval*
North America	125/162 (77.2%)	141/173 (81.5%)	(-14.4%, 2%)
International	254/315 (80.6%)	268/317 (84.5%)	(-9.4%, 2.2%)

*of difference in success rates between Moxifloxacin and comparator (Moxifloxacin – comparator)

Table 15: Clinical Success Rates by Pathogen in Patients with Complicated Skin and Skin Structure Infections

Pathogen	Megaxin IV / Megaxin Tablets n/ N (%)	Comparator n/N (%)
<i>Staphylococcus aureus</i> (methicillin- susceptible isolates) ^a	106/129 (82.2%)	120/137 (87.6%)
<i>Escherichia coli</i>	31/38 (81.6 %)	28/33 (84.8 %)
<i>Klebsiella pneumoniae</i>	11/12 (91.7 %)	7/10 (70%)
<i>Enterobacter cloacae</i>	9/11 (81.8%)	4/7 (57.1%)

a) methicillin susceptibility was only determined in the North American Study

14.7 Complicated Intra-Abdominal Infections

Two randomized, active controlled trials of cIAI were performed. A double-blind trial was conducted primarily in North America to compare the efficacy of sequential IV/PO Megaxin 400 mg QD for 5-14 days to IV/ piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of patients with cIAI, including peritonitis, abscesses, appendicitis with perforation, and bowel perforation. This study enrolled 681 patients, 379 of which were considered clinically evaluable. A second open-label international study compared Megaxin IV / Megaxin Tablets 400 mg QD for 5-14 days to IV ceftriaxone plus IV metronidazole followed by PO amoxicillin/clavulanic acid in the treatment of patients with cIAI. This study enrolled 595 patients, 511 of which were considered clinically evaluable. The clinically evaluable population consisted of subjects with a surgically confirmed complicated infection, at least 5 days of treatment and a 25-50 day follow-up assessment for patients at the Test of Cure visit. The overall clinical success rates in the clinically evaluable patients are shown in **Table16**.

Table 16: Clinical Success Rates in Patients with Complicated Intra-Abdominal Infections

Study	Megaxin IV / Megaxin Tablets n/ N (%)	Comparator n/N (%)	95% Confidence Interval^a
North America (overall)	146/183 (79.8 %)	153/196 (78.1 %)	(-7.4%, 9.3%)
Abscess	40/57 (70.2 %)	49/63 (77.8 %) ^b	NA ^c
Non-abscess	106/126 (84.1 %)	104/133 (78.2 %)	NA
International (overall)	199/246 (80.9 %)	218/265 (82.3 %)	(-8.9 %, 4.2%)
Abscess	73/93 (78.5 %)	86/99 (86.9 %)	NA
Non-abscess	126/153 (82.4 %)	132/166 (79.5 %)	NA

a) of difference in success rates between Megaxin IV / Megaxin Tablets and comparator (Megaxin IV / Megaxin Tablets – comparator)

b) Excludes 2 patients who required additional surgery within the first 48 hours.

c) NA - not applicable

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Megaxin Tablets

Megaxin (moxifloxacin) hydrochloride tablets are available as oblong, dull red film-coated tablets containing 400 mg moxifloxacin.

The tablet is coded with the word “BAYER” on one side and “M400” on the reverse side.

PP/Aluminium foil blisters in cartons of 5, 7, 10 film-coated tablets.

Store below 25°C; store in the original package in order to protect from moisture.

16.2 Megaxin IV

Megaxin IV (moxifloxacin) hydrochloride in sodium chloride injection is available as infusion bottles 250 ml of colourless glass (type 2) sealed with chlorbutyl grey mat with foil-clad PTFE siliconized type 1 infusion stoppers and containing 400 mg of moxifloxacin in 0.8% saline.

NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

Parenteral drug products should be inspected visually for particulate matter prior to administration. Samples containing visible particulates should not be used.

Because the containers are for single-use only, any unused portion should be discarded.

Do not store below 15° C

17 PATIENT COUNSELING INFORMATION

Antibacterial Resistance

Antibacterial drugs including Megaxin IV / Megaxin Tablets should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When Megaxin IV / Megaxin Tablets 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 Megaxin IV / Megaxin Tablets or other antibacterial drugs in the future.

Administration With Food, Fluids, and Drug Products Containing Multivalent Cations

Patients should be informed that Megaxin tablets may be taken with or without food. Patients should be advised to drink fluids liberally.

Megaxin 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 VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution.

Serious and Potentially Serious Adverse Reactions

Patients should be informed of the following serious adverse reactions that have been associated with Megaxin IV / Megaxin Tablets 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 Megaxin IV / Megaxin Tablets 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 Megaxin IV / Megaxin Tablets 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:** Megaxin IV / Megaxin Tablets may produce changes in the electrocardiogram (QTc interval prolongation). Megaxin IV / Megaxin Tablets should be avoided in patients receiving Class IA (for example quinidine, procainamide) or Class III (for example amiodarone, sotalol) antiarrhythmic agents. Megaxin IV / Megaxin Tablets 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 Megaxin IV / Megaxin Tablets.
- **Hypersensitivity Reactions:** Patients should be advised that Megaxin IV / Megaxin Tablets may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose. Patients should discontinue Megaxin IV / Megaxin Tablets 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 Megaxin IV / Megaxin Tablets if there is a history of this condition. Patients should also inform their physician if they are taking NSAIDs concurrently with Megaxin IV / Megaxin Tablets.
- **Neurologic Adverse Effects (for example, dizziness, lightheadedness):** Megaxin IV / Megaxin Tablets may cause dizziness, lightheadedness and vision disorders; 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.
- **Psychotic Reaction:** Psychotic reactions sometimes resulting in self-injurious behavior have been reported in patients receiving fluoroquinolones. Patients should notify their physician if they have a history of psychiatric illness before taking Megaxin IV / Megaxin Tablets.
- **Peripheral Neuropathies:** Patients should be informed that peripheral neuropathy has been associated with Megaxin IV / Megaxin Tablets use. Symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should discontinue Megaxin IV / Megaxin Tablets and contact their physician.

- **Blood Glucose Disturbances:** Inform the patients that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue Megaxin IV / Megaxin Tablets and consult a physician.
- **Photosensitivity/Phototoxicity:** Patients should be informed that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking Megaxin IV / Megaxin Tablets. If patients need to be outdoors while using Megaxin IV / Megaxin Tablets, 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.

MANUFACTURER: Bayer Pharma AG, Leverkusen, Germany.

REGISTRATION HOLDER: Bayer Israel Ltd, 36 Hacharash St., Hod Hasharon 45240.

Change history:

- 03/2012- Updated according to FDA leaflet correlating to CCDS 17. It was submitted as הצעת עלון חדשה.
The reason we have decided to update the leaflet according to the FDA leaflet is following Dr.Tal Lavy request to include Myasthenia Gravis warning in the black box label. Approved 3/2012.
- Updated according to US NDA 021085 correlated to CCDS # 18 variation # 4293 submitted 02/01/2013.
- 11/2013- updated according to FDA approved 19/8/2013. Not CCDS event. This update includes also the update from 01/2013 CCDS #18. Approved 18.03.2014
- Updated according to EMA-PRAC-July-2014, submitted 16/07/14, approved 24/08/14
- Updated according to USA PI dated Nov-2014 (correlated to CCDS#19 variation 6411), submitted 29/03/15, approved 28/01/16.