SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: SERIOUS ADVERSE REACTIONS, INCLUDING TENDINITIS AND TENDON Rupture, PERIPHERAL NEUROPATHY, EFFECTS OF CENTRAL NERVOUS SYSTEM AND VIOLENCE OF MYASTENIA GRAVIS

Fluoroquinolones, including POL-MOXİ, can cause disabling and irreversible adverse reactions such as:

o Tendonitis and tendon rupture
o Peripheral neuropathy
o Central nervous system effects

In patients with any of these reactions, use of POL-MOXİ should be discontinued immediately and fluoroquinolone should be avoided.

Fluoroquinolones, including POL-MOXİ, may exacerbate muscle weakness in patients with myasthenia gravis. Use of POL-MOXİ should be avoided in patients with a known history of myasthenia gravis.

Since the fluoroquinolone group drugs, including POL-MOXİ, are known to be associated with serious adverse reactions, the following indications may be used if there are no other alternatives.

o Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE HUMAN MEDICINAL PRODUCT

POL-MOXİ 400 mg/250 ml Solution For IV Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Moxifloxacin 400 mg (as hydrochloride)
Excipients:
Sodium Chloride 2 g
(250 ml of solution for infusion contains 34 mmol sodium) For excipients see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, slightly yellow, homogeneous solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluoroquinolones, including POL-MOXİ, should not be used because of the risk of serious adverse effects in the presence of alternative treatment options for acute bacterial exacerbation of chronic bronchitis.

Official guidelines on the correct use of antibacterial drugs should be considered. POL-MOXİ should only be used for the treatment of infections that have been proven to be susceptible to susceptible bacteria or that have serious suspicion.

POL-MOXİ is indicated for the treatment of the following bacterial infections caused by susceptible strains.

Acute exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus, Moraxella catarrha*lis;

Streptococcus pneumoniae (including penicillin-resistant strains with MIC of ≥ 2 µg / ml for penicillin), *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* pneumonia derived from the community; including **community-acquired pneumonia** caused by multidrug-resistant strains *;

Streptococcus pneumoniae with multiple drug resistance, such as penicillin-resistant S. Pneumoniae strains and strains resistant to two or more of the following antibiotics: penicillin (MIC value ≥ 2 µg/ml), 2nd generation cephalosporins (eg, cefurixime), macrolides, tetracyclines and trimethoprim / sulfamethoxazole.

In uncomplicated skin and soft tissue infections caused by *Staphylococcus aureus, Streptococcus pyogenes*;

Complicated skin and soft tissue infections (including diabetic foot) caused by methicillin-sensitive *Staphlylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae*;

In complicated **intraabdominal infections** caused by *Escherichia coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteriodes thetaiotaomicron or Peptostreptococcus spp.*

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

4.2 Posology and method of administration
Posolgy
The duration of treatment should be determined by the severity of the indication or the clinical response. The following general recommendations are made for the treatment of upper and lower respiratory infections:
In clinically indicated cases, treatment can be started with intravenous administration and continued with oral film-coated tablet administration.
Acute exacerbation in chronic bronchitis: 5 days
Community-acquired pneumonia: Recommended treatment duration for sequential administration (oral administration following intravenous administration): 7-14 days
Uncomplicated skin and soft tissue infections: 7 days
Sequential treatment time for complicated skin and soft tissue infections (oral administration following intravenous administration): 7-21 days.
Sequential treatment for complicated intraabdominal infections (oral administration following intravenous administration): 5-14 days.
The duration of treatment should not be exceeded for the indication being treated. In clinical studies (complicated skin and soft tissue infections), POL-MOXİ has been investigated for up to 21 days of treatment.
Route of administration:
For intravenous use; constant infusion over 60 minutes.

If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions.

The following solutions has been shown to compatible with POL-MOXİ at room temperature for 24 hours stable.

Water for injection
0.9% sodium chloride
1 M sodium chloride
5% glucose
10% glucose
40% glucose
20% xylitol
Ringer solution
Lactated ringer solution

POL-MOXİ be given with another drug, two drugs should be administered separately.

Only clear solution should be used.

Special populations
Renal/hepatic impairment
No adjustment of dosage is required in patients with mild to severely impaired renal function (included creatinine clearance ≤ 30 mL/min/l.73m^2) or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

There is insufficient data in patients with impaired liver function (see section 4.3).

Geriatric population:
No adjustment of dosage is required in the elderly.

Paediatric population:
Efficacy and safety of moxifloxacin in children and adolescents have not been established (see section 4.3).

Others:
No adjustment of dosage is required in the ethnic groups.

4.3 Contraindications
- Hypersensitivity to moxifloxacin, other quinolones or to any of the excipients
- Pregnancy and lactation
- Patients below 18 years of age.
- Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Moxifloxacin should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

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

4.4 Special warnings and precautions for use

Tendinitis and tendon rupture, causing including peripheral neuropathy and central nervous system effects and potential irreversible disability serious adverse reactions.

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

These reactions can occur within hours or weeks after starting POL-MOXİ. Patients of all age groups or patients without pre-existing risk factors experienced these adverse reactions.
In the event of the first signs or symptoms of any serious adverse reactions, POL-MOXİ should be discontinued immediately. In addition, the use of fluoroquinolones, including POL-MOXİ, should be avoided in patients experiencing any of these serious adverse reactions in connection with fluoroquinolones.
Acute bacterial exacerbation of chronic bronchitis should be preferred when treatment with another agent is not possible.

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

Treatment with moxifloxacin should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.

Moxifloxacin should be used with caution in patients with any condition pre-disposing to cardiac arrhythmias (e.g. acute myocardial ischaemia) because they may have an increased risk of developing ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. See also sections 4.3 and 4.5.

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

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

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

<u>Hypersensitivity/allergic reactions</u>

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

Severe liver disorders
Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

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

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

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of a potentially irreversible condition (see section 4.8).

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

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

initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

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

Myasthenia Gravis aggravation:
Fluoroquinolones have neuromuscular blockade activity and may exacerbate muscle weakness in patients with myasthenia gravis. In patients with myasthenia gravis using fluoroquinolone, severe post-marketing adverse events involving ventilatory support and death have been associated with fluoroquinolone. Patients with a history of myasthenia gravis should avoid the use of fluoroquinolone (see section 4.8).
Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment (see sections 4.3 and 4.8). The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

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

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Dysglycemia
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with moxifloxacin (see section 4.8). In moxifloxacin-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitivity reactions
Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.

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 should be used with caution in these patients.

Peri-arterial tissue inflammation
Moxifloxacin solution for infusion is for intravenous administration only. Intra-arterial administration should be avoided since preclinical studies demonstrated peri-arterial tissue inflammation following infusion by this route.
Patients with special cSSSI
Clinical efficacy of moxifloxacin in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Patients on sodium diet
This medicinal product contains 787 mg (approximately 34 mmol) in each dose. This should be considered for patients on a controlled sodium diet.

Interference with biological tests
Moxifloxacin therapy may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving moxifloxacin.

Patients with MRSA infections
Moxifloxacin is not recommended for the treatment of MRSA infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see section 5.1).

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

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions with medicinal products
An additive effect on QT interval prolongation of moxifloxacin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore, co-administration of moxifloxacin with any of the following medicinal products is contraindicated (see also section 4.3):
- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (saquinavir, sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels (e.g. loop and thiazide-type diuretics, laxatives and enemas [high doses], corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

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

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

Changes in INR:
A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibacterial agents, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Even an interaction is not seen with warfarin, a precautionary measure would be to more frequently monitor the INR. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.
Clinical studies have shown no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole.
In vitro studies with human cytochrome P450 enzymes supported these findings. Considering these results a metabolic interaction via cytochrome P450 enzymes is unlikely.

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

Pediatric population:
The effectiveness and safety of POL-MOXI in children and adolescents has not been established (see also Section 4.3).

4.6 Pregnancy and lactation
General recommendations
Pregnancy category: C

Women of childbearing potential /Contraception

Clinical data on animal studies do not indicate impaired fertility (see section 5.3 Preclinical safety data).

Pregnancy
The safety of moxifloxacin in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity.The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals and reversible joint injuries described in children receiving some fluoroquinolones, POL-MOXI must not be used in pregnant women (see section 4.3).

Lactation
There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breast-feeding is contraindicated with POL-MOXI. (see section 4.3).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects
Adverse observed in clinical trials and derived from post-marketing reports with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:
Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
Very Common (≥1/10)
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000),
Unknown(cannot be estimated from available data)

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

Blood and lymphatic system disorders
Uncommon: Anaemia, leucopenia(s), neutropenia, thrombocytopenia, thrombocythemia, blood eosinophilia, prothrombin time prolonged/ INR increased
Rare: Anormal thromboplastin level
Very rare: Prothrombin level increased/ INR decreased, Agranulocytosis

Immune system disorders
Uncommon: Allergic reaction (see section 4.4)
Rare: Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema/ angiooedema (incl. laryngeal oedema, potentially life-threatening, see section 4.4)

Metabolism and nutrition disorders
Uncommon: Hyperlipidemia
Rare: Hyperglycemia, hyperuricemia
Very rare: Hypoglycemia

Psychiatric disorders
Uncommon: Anxiety reactions, psychomotor hyperactivity/ agitation
Rare: Emotional lability, depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts), hallucination (see section 4.4)
Very rare: Depersonalization psychotic reactions (potentially culminating in self- injurious behaviour, such as suicidal ideations/ thoughts, or suicide attempts) (see section 4.4)

Nervous system disorders
Common: Headache, dizziness
Uncommon: Par- and Dysaesthesia, taste disorders (incl. ageusia in very rare cases), confusion and disorientation, sleep disorders (predominantly insomnia), tremor, vertigo, somnolence
Rare: Hypoaesthesia, smell disorders (incl. anosmia), abnormal dreams, disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo), seizures incl. grand mal convulsions (see section 4.4), disturbed attention, speech disorders, amnesia, peripheral neuropathy and polyneuropathy
Very rare: Hyperaesthesia

Eye disorders
Uncommon: Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)
Very rare: Transient loss of vision (especially in the course of CNS reactions)

Ear and labyrinth disorders
Rare: Tinnitus, hearing impairment incl. deafness (usually reversible)

Cardiac disorders
Common: QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)
Uncommon: QT prolongation,Palpitations,Tachycardia,Atrial fibrillation, Angina pectoris(see section 4.4)
Rare: Ventricular tachyarrhythmias, syncope (i.e., acute and short lasting loss of consciousness)
Very rare: unspecified arrhythmias, Torsade de Pointes (see section 4.4), cardiac arrest

Vascular disorders
Uncommon: Vasodilatation
Rare: Hypertension, Hypotension
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea (including asthmatic conditions)

Gastrointestinal disorders
Common: Nausea, vomiting, gastrointestinal and abdominal pains, diarrhoea
Uncommon: Decreased appetite and food intake, constipation, dyspepsia, flatulence, gastritis, increased amylase
Rare: Dysphagia, stomatitis, antibiotic associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications see section 4.4)

Hepatobiliary disorders
Common: Increase in transaminases
Uncommon: Hepatic impairment (incl. LDH increase), increased bilirubin, increased gamma-glutamyl-transferase, increase in blood alkaline phosphatase
Rare: Jaundice, hepatitis (predominantly cholestatic)
Very rare: Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases see section 4.4)

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, rash, urticaria, dry skin
Very rare: Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening section 4.4)

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia
Rare: Tendonitis, muscle cramp, muscle twitching, muscle weakness
Very rare: Tendon rupture, arthritis, muscle rigidity, exacerbation of symptoms of myasthenia gravis

Renal and urinary disorders
Uncommon: Dehydration
Rare: Renal impairment (incl. increase in BUN and creatinine), renal failure

General disorders and administration site conditions
Common: Injection and infusion site reactions
Uncommon: Feeling unwell (predominantly asthenia or fatigue), painful conditions (incl. pain in back, chest, pelvic and extremities), sweating, infusion site (thrombo-) phlebitis
Rare: Oedema

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

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

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions.

4.9 Overdose
No specific countermeasures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400 mg oral or intravenous moxifloxacin will reduce systemic availability of the drug by more than 80% or 20% respectively. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

5. PHARMACOLOGIC PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones
ATC code: J01MA14

Mechanism of action
Moxifloxacin inhibits bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) that are required for bacterial DNA replication, transcription and repair.

PK/PD
Fluoroquinolones exhibit a concentration dependent killing of bacteria. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials indicate that the primary determinant of efficacy is the AUC_{24}/MIC ratio.

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

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

Breakpoints
EUCAST clinical MIC and disk diffusion breakpoints for moxifloxacin (01.01.2011):

Organism	Susceptible	Resistant
Staphylococcus spp.	≤0,5 mg/l ≥24 mm	>1 mg/l <21 mm
S. pneumoniae	≤0,5 mg/l ≥22 mm	>0,5 mg/l <22 mm
Streptococcus groups A, B, C, G	≤0,5 mg/l ≥18 mm	>1 mg/l <15 mm

H. influenza	≤0,5 mg/l ≥25 mm	>0,5 mg/l ≥25 mm
M. catarrhalis	≤0,5 mg/l ≥23 mm	>0.5 mg/l <23 mm
Enterobacteriaceae	≤0,5 mg/l ≥20 mm	>1 mg/l <17 mm
Non-species related breakpoints**	≤0,5 mg/l	>1 mg/l
* Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where interpretative criteria remain to be determined.		

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

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus*+ Streptococcus agalactiae* (Group B) Streptococcus milleri group* (*S. anginosus, S. constellatus* ve *S. intermedius*) *Streptococcus pneumoniae* Streptococcus pyogenes**(Group A) *Streptococcus viridans* group (*S. viridans, S. mutans, S. mitis, S. sanguinis, S. salivarius, S. thermophilus*)
Aerobic Gram-negative micro organisms *Acinetobacter baumanii Haemophilus influenzae* Legionella pheumophila* *Moraxella (Branhamella) catarrhalis**
Anaerobic micro-organisms *Prevotella spp.*
"Other" micro-organisms *Chlamydophila* (*Chlamydia*) *pneumoniae* Coxiella burnetii* *Mycoplasma pneumoniae**
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* Enterococcus faecium**
Aerobic Gram-negative micro-organisms *Enterobacter cloacae* Escherichia coli*# Klebsiella pneumoniae*# Proteus mirabilis**
Anaerobic micro-organisms *Bakterioides fragilis**

Inherently resistant organisms
Aerobik Gram-negatif Mikro-organizmalar
Pseudomonas aeruginosa

*Activity has been satisfactorily demonstrated in clinical studies.
[+]Methicillin resistant *S. aureus* have a high probability of resistance to fluoroquinolones.
Moxifloxacin resistance rate of > 50% have been reported for methicillin resistant *S. aureus*.
[#]ESBL-producing strains are commonly also resistant to fluoroquinolones.

5.2 Pharmacokinetic properties

General Features

Absorption and Bioavailability

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

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

Distribution:

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

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

Biotransformation:

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal (approximately 40%) and biliary/faecal (approximately 60%) pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.
In clinical Phase I and in vitro studies no metabolic pharmacokinetic interactions with other drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes were observed. There is no indication of oxidative metabolism

Elimination:

Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Following a 400 mg intravenous infusion recovery of unchanged drug from urine was approximately 22% and from faeces approximately 26%. Recovery of the dose

(unchanged drug and metabolites) totalled to approximately 98% after intravenous administration of the drug. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys. Concomitant administration of moxifloxacin with ranitidine or probenecid did not alter renal clearance of the parent drug.

Renal impairment
The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance > 20 ml/min/1.73 m2). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m2).

Hepatic impairment
On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function.

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

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

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

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

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

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

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

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

Quinolones, including moxifloxacin, are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
0,1 N Sodium hydroxide solution
0,1 N Hydrochloric acid solution
Water for injections

6.2 Incompatibilities

The following solutions are incompatible with POL-MOXİ:
Sodium chloride 10% and 20% solutions
Sodium bicarbonate 4.2% and 8.4% solutions

6.3 Shelf life

2 years

6.4 Special precautions for storage

Please store it at room temperature under 25°C.
At temperatures below 15 ° C, at room temperature (15 ° C - 25 ° C) redissolution precipitation may occur.Therefore, it is not recommended to store *POL-MOXİ* in the refrigerator.

6.5 Nature and contents of packaging

PP Bag, 250 ml
It has two forms, namely the forms with and without sets.

6.6 Destruction of the residual materials human medicinal product and other special precautions

The unused or waste products must be discarded according to the “Regulation Related to the Control of Medical Wastes” and the “Regulation Related to the Control of Packaging and Packaging Wastes”.

Do not use if there are any visible particulate matter or if the solution is cloudy

7. MARKETING AUTHORISATION HOLDER

POLİFARMA İLAÇ SANAYİ VE TİC. A.Ş.
Vakıflar OSB Mahallesi, Sanayi Caddesi, No:22/1
Ergene/TEKİRDAĞ

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