# **JOYLOXIN** FILM COATED TABLET



## Moxifloxacin 400 mg

## COMPOSITION

Each film-coated tablet contains Moxifloxacin HCI · · · · ·

(as Moxifloxacin 400 mg)

Excipients: Microcrystalline Cellulose, Lactose Monohydrate, Croscarmellose Sodium, Magnesium stearate, Hypromellose 2910, Dehydrated Alcohol, Purified Water, Opadry White OY-C-7000A, Ferric Oxide (Red), Methylene Chloride, Dehydrated Alcohol

Evaporated during manufacturing

### DESCRIPTION

Pink, oblong film-coated tablet

### Moxifloxacin has been shown to be active against most strains of the following microorganisms:

<u>Gram-positive bacteria</u>: Enterococcus faecalis (many strains are only moderately susceptible), Staphylococcus aureus (including methicillin-susceptible strains), Steptococcus milleri group (streptococcus anginosus, Streptococcus constellatus), Streptococcus pneumonia (including penicillin and macrolide resistant strains), Streptococcus pyogenes (A group), Streptococcus perincial and machinic resistant strains), streptococcus yogenes (A group), streptococcus mittor, Streptococcus agalactiae, Streptococcus dysgalactiae, Staphylococcus cohnii, Staphylococcus epidermidis (including methicillin-susceptible strains), Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus, Staphylococcus simulans.  $\underline{Gram-negative\ bacteria\ :}\ Haemophilus\ influenza\ (including\ \beta\ -lactamase\ negative\ and\ positive\ -lactamase\ negative\ and\ positive\ -lactamase\ negative\ and\ positive\ -lactamase\ negative\ and\ positive\ -lactamase\ negative\ -lactamase\ negative\ -lactamase\ negative\ -lactamase\ -$ Strains), Haemophilus parainfluenzae, Klebsiella pneumonia, Moraxella catarrhalis (including  $\beta$ -lactamase negative and positive strains), E.coli, Enterobacter cloacae, Bordetella pertussis, Klebsiella oxytoca, Enterobacter aerogenes, Enterobacter intermedius, Enterobacter sakazaki, Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia rettgeri, Providencia stuartii, Neisseria gonorrhoeae.

Atypicals: Chlamydia pneumonia, Mycoplasma pneumonia, Mycoplasma hominis, Mycoplasma Amerobic bacteria: Bacteroides distasonis, Bacteroides fragilis, Bacteroides ovatus, Bacteroides

thetaiotaomicron, Bacteroides uniformis, Fusobacterium spp., Porphyromonas spp., Porphyromonas anaerobius, Porphyromonas asaccharolyticus, Porphyromonas magnus, Prevotella spp., Propionibacterium spp., Clostridium perfringenis, Peptostreptococcus species.

### INDICATIONS

JOYLOXIN tablets are indicated for the treatment of the following bacterial infections caused by bacteria susceptible to moxifloxacin

Acute bacterial sinusitis caused by Streptococcus pneumoniae, Haemophilus influenzae or

Moraxella catarrhalis

- Acute bacterial exacerbations of chronic bronchitis <u>caused by Streptococcus pneumoniae.</u> Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae or Moraxella

- Community acquired pneumonia (of mild to moderate severity) caused bt Streptococcus Haemophilus influenzae, Mycoplasma pneumoniae, chlamydia pneumonae or
- Moraxella catarrhalis
   Uncomplicated skin and skin structure infections caused by Staphylococcus aureus or Streptococcus pyogenes
- Complicated skin and skin structure infections caused by methicillin-susceptible Staptococcus

- Complicated skill and skill studential integrals caused by medianisms acceptable supplied agrees, Escherichia colli, Klebsiella pneumoniae or Enterobactericiacae JOYLOXIN tablets should not be used to initiate therapy for any type of skin and skin structure

infection or in severe community-acquired pneumonia

- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.

JOYLOXIN tablets are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae. Joyloxin 400mg tablets are indicated for the treatment of the above infections if they are caused by bacteria susceptible to moxifloxacin

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

## DOSAGE AND ADMINISTRATION

The recommended dose is one 400 mg film-coated tablet once daily.

Renal/hepatic impairment

No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. There is insufficient data in patients with impaired liver function.

Other special populations

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

Paediatric population

Moxifloxacin is contraindicated in children and adolescents (< 18 years). Efficacy and safety of

moxifloxacin in children and adolescents have not been established.

Method of administration

The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

Duration of administration

JOYLOXIN tablets should be used for the following treatment durations:

- Acute exacerbation of chronic bronchitis	5 - 10 days			
- Community acquired pneumonia	10 days			
- Acute bacterial sinusitis	7 days			
- Mild to moderate pelvic inflammatory disease	14 days			

JOYLOXIN tablets have been studied in clinical trials for up to 14 days treatment.

Sequential (intravenous followed by oral) therapy
In clinical studies with sequential therapy most patients switched from intravenous to oral therapy within 4 days (community-acquired pneumonia) or 6 days (complicated skin and skin structure infections). The recommended total duration of intravenous and oral treatment is 7 -14 days for community-acquired pneumonia and 7 -21 days for complicated skin and skin structure infections. The recommended dose (400 mg once daily) and duration of therapy for the indication being treated should not be exceeded.

### WARNING AND PRECAUTIONS

The benefit of moxifloxacin treatment especially in infections with a low degree of severity should be balanced with the information contained in the warnings and precautions section

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions
Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some
patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec  $\pm$  26 msec, 1.4% compared to baseline. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT

Medication that can reduce potassium levels should be used with caution in patients receiving

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. torsade de pointes) and cardiac arrest. The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

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

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

Treatment with Joyloxin should be avoided due to the lack of clinical experience with the drug in these patient populations:

- o In patients with known prolongation of the QT interval
- o In patients with uncorrected hypokalemia
  o In patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents

## Severe liver disorders

Cases of fullminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin. 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

Due to limited clinical data the use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).

### Serious bullous skin reactions

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

## Patients predisposed to seizures

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

### Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. 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 an irreversible condition 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. In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Antibiotic-associated diarrhoea incl. colitis

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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

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

## Tendon inflammation, tendon rupture

Tendon inflammation and rupture (especially Achilles tendon), sometimes bilateral, may occur with quinolone therapy including moxifloxacin, even within 48 hours of starting treatment and have been reported up to several months after discontinuation of therapy. The risk of tendinitis and tendon rupture is increased in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin, rest the affected limb(s) and consult their doctor immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon.

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Aortic aneurysm and dissection

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, vascuta Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet'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. immediately consult a physician in an emergency department. 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.

Dysglycemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with moxifloxacin. 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. 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 qlucose-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.

<u>Patients with pelvic inflammatory disease</u>
For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with JOYLOXIN tablets is not recommended.

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

Patients with special cSSSi Clinical efficacy of intravenous moxifloxacin in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

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

Paediatric population
Due to adverse effects on the cartilage in juvenile animals the use of moxifloxacin in children and

# adolescents < 18 years is contraindicated. <u>Information about excipients</u>

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say

essentially "sodium-free".

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

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

<u>Aortic aneurysm or dissection</u>
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 aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection, 6 in presented to the control of the predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet'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.

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

<u>Blood Glucose Disturbances</u>
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with JOYLOXIN TABLET. In JOYLOXIN TABLET-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (for example, sulfonylurea) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue JOYLOXIN TABLET and initiate appropriate therapy Immediately.

## Aortic aneurysm or dissection and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Therefore, fluoroguinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis) or
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or
- for heart valve regurgitation/incompetence (e.g. infective endocarditis)

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

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

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

### CONTRAINDICATIONS

- 1) Patients with a history of hypersensitivity to moxifloxacin, other quinolones or to any of the exipients.
- Children and adolescents below 18 years of age (Efficacy and safety in children and adolescents have not been established).
- 3) Pregnancy and lactation.4) Patients with impaired liver function (Due to limited clinical data).
- 5) Patients with transaminases increase > 5fold ULN.
  6) Patients with a history of tendon disease/disorder related to quinolone treatment.
- 7) Patients with known prolongation of the QT interval.
  8) Patients with electrolyte disturbances (Particularly in uncorrected hypokalaemia).
- 9) Patients with bradycardia, a history of symptomatic arrhythmias.

  10) Patients with heart failure with reduced left-ventricular ejection fraction

11) Patients receiving anti-arrhythmics Class IA (for example quinidine, procainamide) or Class III (for example amiodarone, sotalol), antipsychotics, 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).

- 1) Patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold. (Seizures may occur with quinolone therapy).
- 2) Moxifloxacin should be used with caution as an additive effect of moxifloxacin on the QT
- interval cannot be excluded for the following conditions:
   Patients with ongoing proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.
- Patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded. Women and elderly patients who, both may be more susceptible to QTc prolonging medications.

- 3) Patients with myasthenia gravis (the symptoms can be exacerbated).
  4) 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).

### ADVERSE REACTIONS

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1) Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential [IV/oral]/intravenous only administration) sorted by CIOMS III categories of frequency (overall n= 17,951, including n = 4,583 from sequential/intravenous therapy studies) are listed below: ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhea.

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

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/10), rare (≥ 1/10,000 to < 1/10,00),

very rare (< 1/10,000).							
System Organ Class	Common	Uncommon	Rare	Very Rare			
Infections and Infestations	Mycotic Superinfections						
Blood and the Lymphatic System Disorders		Anaemia, Leukopaenia(s), Neutropaenia, Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged / INR increased	Thromboplastin level abnormal	Prothrombin level increased / INR decreased Prothrombin level / INR abnormal			
Immune System Disorder		Allergic reaction, Pruritus,Rash, Urticaria, Blood eosinophilia	Anaphylactic / Anaphylactoid reaction Allergic cedema / Angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic / anaphylactoid shock (potentially life threatening)			
Metabolism and Nutrition Disorders		Hyperlipidemia	Hyperglycaemia Hyperuricaemia	Hypoglycaemia			
Psychiatric Disorder		Anxiety reactions Psychomotor hyperactivity / Agitation	Emotional lability Depression (in very rare case potentially culminating in self-injurious behavior, such as suicidal ideation/thoughts or suicide attempts)	Depersonalisation Psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideation/thoughts or suicide attempts)			
Nervous System Disorders	Headache Dizziness	Par-and Dysesthesia Taste disorders (incl. ageusia in very rare cases) Confusion Disorientation Sleep disorders Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders	Hyperaesthesia			

			Amnesia Peripheral neuropathy (that may be irreversible) and polyneuropathy	
Eye Disorder		Visual disturbances (esp. in the course of CNS reactions)		Transient loss of vision (esp. in the course of CNS reactions)
Ear and Labyrinth Disorder			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorder	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular Tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias Torsade de Pointes Cardiac arrest (esp. in patients with severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia)
Respiratory Thoracic and Mediastinal Disorders		Dyspnoea (incl. asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma- glutamyl-transferase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis potentially leading to life- threatenning liver failure (incl. fatal case)
Skin and Subcutaneous Tissue Disorders				Bullous skin reactions like Stevens-Johnson- Syndrome or Toxic Epidermal Necrolysis (potentially life threatening)
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Tendon rupture Arthritis Gait disturbance (caused by muscular, tendon or joint symptoms) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders		Dehydration (caused by diarrhea or reduced fluid intake)	Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorder)	
General Disorders and Administration Site Conditions	Injection and infusion site reaction	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-)phlebitis		

2) The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Ventricular tachyarrythmias, Hypotension, Oedema, Antibiotic associated colitis (in very rare cases associated with life threatening complications), Seizures of various clinical manifestations (including grand mal convulsions), Hallucination, Renal impairment and Renal failure (due to dehydration especially in elderly with pre-existing renal disorders).

## GENERAL PRECAUTIONS

1) To reduce the development of drug-resistant bacteria and maintain the effectiveness of moxifloxacin, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

2) Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolongation medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval. As the magnitude of QT prolongation may increase with increasing concentrations of moxifloxacin, the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in clinical studies with more than 9000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

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

4) In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately. Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with moxifloxacin has to be discontinued, medical treatment (e.g. treatment for shock) is required.

- 5) Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. At the first sign of pain or inflammation, patients should discontinue treatment and rest the affected limb(s).
- 6) Antibiotics associated colitis has been reported with the use of broad-spectrum antibiotics including moxifloxacin; therefore it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of moxifloxacin. In this clinical situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

  7) Quinolones have been shown to cause photosensitivity reactions in patients. However, in
- specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

  8) For patients with complicated pelvic inflammatory disease (e.g. associated with a tuboovarian
- or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with moxifloxacin is not recommended.
- 9) Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. 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.

  10) Psychiatric reactions may occur even after the first administration of fluoroquinolones,
- including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts. In the event that the patient develops these reactions, Moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if Moxifloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.
- 11) 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.
- 12) Moxifloxacin in vitro activity may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking moxifloxacin.
- 13) Because of the widespread and rising prevalence of fluoroquinolone-resistant Neisseria gonorrhoeae infections, monotherapy with moxifloxacin should be avoided in patients with pelvic inflammatory disease, unless fluoroquinolone-resistant N. gonorrhoeae can be excluded. If fluoroquinolone-resistant N. gonorrhoeae cannot be excluded, the addition of an appropriate antibiotic which is regularly active against N. gonorrhoeae (e.g., a cephalosporin) to empirical moxifloxacin therapy, should be considered.
- 14) Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to
- drive or operate machinery due to CNS reactions and vision disorders

  15) As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with moxifloxacin. In moxifloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemia agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended.

## DRUG INTERACTIONS

Antacids, minerals and multi-vitamins

Concomitant ingestion of Joyloxin together with antacids, minerals and multi-vitamins may result in impaired absorption of moxifloxacin after oral administration due to formation of chelate complexes with the multi-valent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral drugs (e.g. didanosine), and other preparations containing magnesium or aluminium, sucralfate and agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin dose

Warfarin

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

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving anticoagulants concurrently with antibiotics, including Joyloxin The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between Joyloxin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed and, if necessary, the oral anticoagulant dosage should be adjusted as appropriate

<u>Digoxin</u>
The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin and vice versa.

After repeated dosing in healthy volunteers moxifloxacin increased Cmax of digoxin by approximately 30 % at steady state without affecting AUC or trough levels.

Concomitant dosing of charcoal and 400 mg oral Joyloxin reduced the systemic availability of the drug by more than 80 % by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose. After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Food and dairy products

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

An additive effect on QT interval prolongation of moxifloxacin and other medicinal products that An additive effect on QT interval prioringation of moxilioxactin and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes. Therefore co-administration of moxifloxacin with any of the following medicinal products is contraindicated:

-anti-arrhythmics class IA (eg. Quinidine, hydroquinone, disopyramide)

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

## PREGNANCY AND LACTATION

- 1) The safe use of moxifloxacin in human pregnancy has not been established. Reversible joint injuries are described in children receiving some quinolones, however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Consequently, the use of JOYLOXIN during pregnancy is contraindicated.
- 2) As with other quinolones, Moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of JOYLOXIN in nursing mothers is contra-indicated.

## **GERIATRIC USE**

Pharmacokinetics of moxifloxacin are not affected by age. In general, elderly patients may be more susceptible to drug-associated effects of the QT interval. Therefore, moxifloxacin should be avoided in patients taking drugs that can result in prolongation of the QT interval or in patients with risk factors for torsade de pointes.

### OVERDOSE

- Only limited data on overdose are available. Single doses of up to 1200 mg and multiple doses of 600 mg moxifloxacin over 10 days were administered to healthy subjects without any significant undesirable effects.
- 2) In the event of overdosage it is recommended that appropriate supportive care including ECG measurements should be instituted as dictated by the patient's clinical status.

The use of charcoal early after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of overdosage.

3) In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

# SPECIAL PRECAUTIONS FOR STORAGE 1) Keep out of reach of children.

- 2) Do not preserve in other containers in order to avoid accident or quality control problem.

### OTHERS

- 1) As for other quinolones the major toxicological target organs for moxifloxacin were the haemopoietic system (hypocellularity of the bone marrow in dogs and monkeys), the central nervous system (convulsions in monkeys) and the liver (raised liver enzymes, single cell necrosis in rats, dogs and monkeys). These changes were commonly seen only after treatment with high doses of moxifloxacin or after prolonged treatment.
- 2) Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (per os and i.v.) and monkeys (per os) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. Skeletal malformations were observed in rabbits that had been treated with an intravenous dose of 20 mg/kg. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.
- 3) Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

Preserve in well-closed containers. Store at or below 30°C.

## PACKAGE

5 Tablets/Blister × 5 Blisters/Box

Revised in 26th January 2021

