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2. Elements for a Public Summary

2.1 Overview of disease epidemiology

2.1.1 Acute exacerbation of chronic bronchitis

Chronic bronchitis (CB) is a prolonged inflammation in the upper part of the respiratory tract (trachea and bronchi). It is defined by the presence of a mucus producing cough most days of the month, 3 months of a year for 2 successive years. It is not always linked to an infection. An acute exacerbation of chronic bronchitis (AECB) describes a condition with sudden worsening of the inflammation and has been reported at 1.8 per patient per year. The frequency of CB is between 3% and 17% in most developed countries. The mortality in the advanced phase of the disease is 13.4 %, 22% and 35.6% after 0.5, 1 or 2 years after hospitalization for adverse events episodes due to a chronic obstructive lung disease (COPD).

2.1.2 Acute bacterial sinusitis

Rhinosinusitis is defined as "redness/soreness (inflammation) of the nose and the cavity within skull around nose (paranasal sinuses). Characteristic signs and symptoms are either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip). In addition, facial pain/ pressure or loss of smell can be present. Acute bacterial sinusitis (ABS) has been reported to complicate up to 2% of common colds and influenza-like illnesses in adults and up to 10% of such cases in children. In Europe, on average, 8.4% of the Dutch population reported at least one episode of ABS and in Germany 6.3 million diagnosis of acute sinusitis were made between 2000 and 2001. ABS can lead to serious complications, if untreated or undertreated; Furthermore, ABS can evolve into chronic sinusitis, which leads to significant illness.

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2.1.3 Community-acquired pneumonia

Community-acquired pneumonia (CAP) is defined as an inflammation of the lungs that has not been acquired in a hospital or long-term care institution. CAP is an acute condition. Depending on the country and populations studied, CAP may affect 1.6 to 11.6 out of 1000 persons in a given year. Patients over 60 years have a higher risk to develop CAP. The incidence of CAP peaks in the winter season. Up to 61% of patients with CAP are admitted to hospital. The reported death rates of adults admitted to hospital with CAP vary from 6% to 14%. The mortality of patients with severe CAP requiring admission to an Intensive Care Unit is high, varying from 22% to over 50%.

2.1.4 Complicated skin and skin-structure infections

Complicated skin and skin structure infections (cSSSIs) are the most common type of bacterial infection, and can range in severity from mild inflammation to extensive tissue destruction with life-threatening spread of infections inside the body (sepsis). The exact frequency of cSSSIs is unknown. cSSSIs that have been classified as complicated include infected skin ulcers caused by poor blood supply (ischemic ulcers), diabetic foot infections, major abscesses, human or animal bite wound infections, infections involving deeper soft tissues such as surgical or post-traumatic wound infections, and infection of the dead deep layer of the skin (necrotizing fasciitis). Untreated cSSSIs may spread and cause major tissue destruction, bone morrow infection, diabetic foot infection, local amputation or even limb loss and death.

2.1.5 Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is an infection of the female upper genital tract and one of the most common causes of illness among women of childbearing age. It causes acute pain and discomfort and, in many women, leads to long-term problems such as chronic pain, infertility or outside the normal site (ectopic) pregnancy, in addition to its considerable economic cost and psychological stress. The frequency of PID peaks in the age group of 18 to 29 with 88.7 PID hospitalizations per 10,000. More than 90% of hospitalizations for PID occur in 18 to 49-year-old women. The death rate for non-complicated PID is very low. Women with clinically apparent PID are at risk of damage to oviducts (uterine tubes) and subsequent adverse reproductive complications, with PID caused by *Chlamydia* infection being identified as the most important preventable cause of infertility and adverse pregnancy outcome.

2.2 Summary of treatment benefits

Avelox is given for 5 up to 21 days to treat specific types of bacterial infections. It works by killing a wide range of different bacteria that cause the infection. Avelox is taken only once daily and is suitable for single-drug antibiotic treatment.

In several clinical trials and numerous published literatures, Avelox has shown equal efficacy with more rapid symptom relief compared to the comparator drugs.

- Acute exacerbations of chronic bronchitis

The main clinical studies are known as MOSAIC study (630 patients) and MAESTRAL study (1492 patients). The GIANT study with 43,435 patients enrolled (9,225 patients in Europe) confirmed the efficacy and safety of Avelox therapy in AECB under real-life conditions. In patients with AECBs, cure rates from the bacterial infection or improvement with Avelox were generally >90%, and were similar to those achieved with comparators.

- Acute bacterial sinusitis

The SPEED study (192 patients) and the SCALA study (216 patients) showed clinical cure or success in more than 90% of patients. In other studies in acute bacterial sinusitis, the clinical response rate of Avelox ranged from 86% to 96.7%. In the TOPAS studies, a total of 7,090 patients were treated with Avelox in routine clinical practice. Overall, moxifloxacin was assessed as having ‘‘very good’’ or ‘‘good’’ clinical outcome by 94.0–95.3% of physicians.

- Community acquired pneumonia

Several studies enrolled CAP patients requiring hospitalization. These are the TARGET study (662 patients), the MOXIRAPID study (317 patients), the CAPRIE study (401 patients) in elderly patients, and the MOTIV study (748 patients). In summary, Avelox showed cure rates, ranging from 83% to 93%. The early onset of the clinical response seen with Avelox suggests a shortened length of hospital stay and lower treatment costs.

- Complicated skin and skin structure infections

The study by Giordano and colleagues (367 patients), the STIC study (632 patients), and the RELIEF study (670 patients) showed clinical cure rates ranging from 79.4% to 88.7%. The ARTOS study (6594 patients) investigated the efficacy, safety, and tolerability of Avelox under daily-life conditions in patients with cSSSIs. Avelox treatment was associated with rapid relief in symptoms, with 93.2% of patients experiencing either complete resolution of symptoms or improvement at follow-up.

- Mild to moderate pelvic inflammatory disease

In clinical trials, Avelox showed clinical success rates between 78% and 96% as shown in the study reported by Heystek (669 patients) and in the MAIDEN study (741 patients) and MONALISA study (455 patients).

2.3 Unknowns relating to treatment benefits

In the pivotal trials, patients were above 18 years of age, both male and female, in all races, usual co-morbid state and also included elderly (>65 years). There is no evidence to suggest that results would be any different related to age, gender, or race.

Moxifloxacin must not be used in patients under the age of 18 as it has been shown to cause adverse effects on the cartilage of juvenile animals. Efficacy and safety in children and adolescents have not been studied.

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Patients with special cSSSI: Clinical efficacy of intravenous moxifloxacin in the treatment of severe burn infections, fasciitis (infection of deep tissue) and diabetic foot infection with osteomyelitis (infection of the bone marrow) has not been established.

Due to limited clinical data, moxifloxacin must not be used in patients with impaired liver function (severe forms of liver damage called Child Pugh class C) and in patients with increased liver enzymes (transaminases) that are higher than 5 times the upper normal limit.

2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity, anaphylaxis	Based on medical reasoning regarding anaphylactic reactions in general, patients who are sensitized to any quinolone can be assumed to be at increased risk. There is no reliable, validated method to predict this reaction.	No preventive measures known other than avoidance of exposure in patients with a known hypersensitivity history.
Prolongation of QTc interval	QT prolongation is considered as a class effect of fluoroquinolones. Women and elderly patients may also be more susceptible to drug-associated effects on the QT interval. QT prolongation may lead to an increased risk for ventricular arrhythmias. Up to date, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in clinical studies.	Known history of cardiac arrhythmia (QT prolongation), hypokalemia, and additive QT effects of concomitant drugs are to be considered. The recommended dose and the infusion rate (400 mg within 60 minutes) of moxifloxacin should not be exceeded.
Seizure	Fluoroquinolones have the excitatory effects to central nervous system (CNS). In rare cases, this may lead to convulsive seizures in patients with risk factors.	Known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold, concomitant drugs that lower the seizure threshold, electrolyte imbalances, alcohol abuse, or cerebral trauma should be considered.
Peripheral neuropathy	Between 1 patient in every 10,000 to 1 patient in every 1,000 patients treated with moxifloxacin will experience peripheral	No preventive measures known other than inform doctors if patient develop symptoms such as pain,

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	neuropathy and polyneuropathy.	burning, tingling, numbness, or weakness.
Tendinopathy	Tendinitis and tendon rupture are considered as a class effect of fluoroquinolones. Elderly patients and those treated concurrently with corticosteroids are at a high risk of developing tendon inflammation and rupture. Symptoms can occur up to several months after completion of moxifloxacin therapy.	Control of other risk factors for tendinopathy such as tendon disorders history related to quinolone treatment.
Hepatotoxicity	Asymptomatic elevations of transaminases are the common manifestations of drug-induced hepatotoxicity, which are also considered as class effect of fluoroquinolone. Severe liver injury remains rare. Studies showed that the risk of acute liver injury associated with moxifloxacin use is not substantially higher than for several other antimicrobial drugs that are commonly used.	Control risk factors for liver injury such as age, pre-existing liver disease, concurrent medications and excessive alcohol consumption.
Antibiotic associated diarrhea (including colitis) in hospital setting	Antibiotic-associated diarrhea may occur during the use of broad-spectrum antibiotics including moxifloxacin.	No preventive measures known.
Renal failure	A direct nephrotoxic effect of moxifloxacin has not been established. Predisposing factors for developing renal failure during fluoroquinolone therapy are high age, pre-existing renal disorders, administration of other potentially nephrotoxic agents and reduced patient hydration.	Adequate hydration of risk patients maybe has a preventive effect.
Serious vision disorders	The pathophysiology of serious vision disorders induced by moxifloxacin remains unclear. Between 1 patient in every 1,000 to 1 patient in every 100 patients treated with moxifloxacin will experience visual disturbances.	No factors are known to prevent serious vision disorders.
Serious bullous skin reactions	Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin which involves the skin of the body and the mucosa.	The most effective measure to prevent the condition from becoming worse is to recognize it as early as possible and stop giving moxifloxacin.
Depression, suicidality, and psychosis	Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. Between 1 patient in every 100,000 to 1 patient in every 10,000	No preventive measures known.

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	patients treated with moxifloxacin will experience suicide attempts.	
Serious hematological disorders	Between 1 patient in every 1,000 to 1 patient in every 100 patients treated with moxifloxacin will experience anemia, leukopenia(s), neutropenia, thrombocytopenia, thrombocythemia, and prothrombin time prolonged / INR increased.	No preventive measures known.
Exacerbation of myasthenia gravis	Exacerbation of myasthenia gravis is considered as a class effect of fluoroquinolones.	It cannot be completely prevented. However, certain things can be done to reduce the risk: use with caution in patients with myasthenia gravis.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Bradycardia	Decrease in heart rate was observed in animal model. Up to date, no evidence showed that bradycardia is an independent adverse reaction of moxifloxacin.
Rhabdomyolysis, myositis, and myopathy	Fluoroquinolones were suspected to cause rhabdomyolysis. A handful of cases of rhabdomyolysis were reported with the treatment of other fluoroquinolones.
Muscle rupture	Muscle injury, including rupture is a labeled adverse reaction for other fluoroquinolones. Following a request by European Health Authorities the company has agreed to address muscle rupture as an important potential risk or class effect.
Ligament rupture	Fluoroquinolones were suspected to cause ligament rupture. European Health Authorities requested to include ligament rupture in the EU-RMP as an important potential risk.
Selection of drug resistant isolates	In general, Gram-negative and Gram-positive bacteria are susceptible to moxifloxacin. The prevalence of acquired resistance may vary geographically for selected species.
Retinal detachment	Fluoroquinolones were suspected to cause retinal detachment. European Health Authorities requested to include retinal detachment in the EU-RMP as an important potential risk.

Missing information

Risk	What is known
Use of moxifloxacin in children and growing adolescents	The concerns regarding development of resistance and their potential to induce arthropathy in juvenile animals limited the use of quinolones. A development program to evaluate the safety and efficacy of moxifloxacin in children aged 3 months and older in the indication cIAI is ongoing.
Arthropathy (in	Like all other quinolones, moxifloxacin induced arthrotoxicity in juvenile

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pediatric patients)	Beagle dog models. The risk to human is unknown. A development program to evaluate the safety and efficacy of moxifloxacin in children aged 3 months and older is ongoing.

2.5 Summary of additional risk minimization measures by safety concern

No additional risk minimization measures are planned.

2.6 Planned post authorization development plan

List of studies in post authorization development plan

Study/activity (including study number)	**Objectives**	**Safety concerns/efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Phase III randomized, double-blind, multicenter trial to evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin in pediatric subjects with complicated intra-abdominal infection (MOXIPEDIA, Study 11643)	To evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin in pediatric subjects with complicated intra-abdominal infection	Safety in children with special emphasis placed on musculoskeletal AEs and ECG findings.	Ongoing	Clinical study report will be available based on request.
Phase I sequential, non-randomized, non-blinded, non-controlled single dose, multi-center trial to evaluate the safety, tolerability and pharmacokinetic of 5 – 10 mg/kg single 1h infusion of intravenous moxifloxacin in pediatric patients aged 3 months to 14 years (Study 11826)	To evaluate the safety, tolerability and pharmacokinetics of 5–10 mg/kg single 1h infusion of intravenous moxifloxacin in pediatric patients aged 3 months to 14 years	PKs of moxifloxacin in children of different ages; Safety and tolerability of single dose IV moxifloxacin in children	Ongoing	Clinical study report will be available based on request.

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Phase III randomized placebo-controlled, double-blind trial comparing 2 treatment shortening regimens with the standard regimen for the treatment of adults with pulmonary tuberculosis (REMoxTB, Study 12971)	To compare 2 treatment shortening regimens with the standard regimen for the treatment of adults with pulmonary tuberculosis	Efficacy in adults with pulmonary tuberculosis	Ongoing	Clinical study report will be available based on request.

Studies which are a condition of the marketing authorization

None of the above studies is a condition of the marketing authorization.

2.7 Summary of changes to the Risk Management Plan over time

Table 2-1: Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1	31 May 2007	**Important Identified Risks:** QTc prolongation and Torsade de pointes, Hypersensitivity/Anaphylaxis. **Important potential risks:** Bradycardia, Hypoglycemia, Antibiotic-associated diarrhea (including colitis) in hospital setting **Missing information**: Use in children and growing adolescent	
2	11 January 2008	Seizure, tendinopathy, hepatotoxicity, renal failure, serious vision disorders, serious bullous skin reactions, depression, suicidality and psychosis, serious haematological disorders, exacerbation of myasthenia gravis, rhabdomyolysis, myositis and myopathy were added as “important potential risks”. Hypoglycemia, photosensitivity and hemolysis in patients with	Several topics have been added to the section of “newly identified safety concerns” since Version 01 of this document in an attempt to follow more closely the evolving regulatory guidelines on risk management plans, and/or in response to a request from BfArM (as the RMS) in the PSUR Final Assessment Report

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		G6PD deficiency were added to evaluated topics currently not classified as safety concerns.	issued for the 15th + 16th (oral) /10th + 11th (iv) moxifloxacin PSUR.
3	20 October 2009	Peripheral neuropathy and selection of drug resistant isolates were added as potential risks. In addition, arthropathy (in pediatric patients) was added as "missing information". Seizure, tendinopathy, hepatotoxicity, renal failure, serious vision disorders, serious bullous skin reactions, depression, suicidality and psychosis, serious haematological disorders, exacerbation of myasthenia gravis were removed as "important potential risks" and were added as "important identified risks".	Peripheral neuropathy and selection of drug resistant isolates were added as additional risks on request of the BfArM (as the RMS) in the Final Assessment Report issued for the EU Risk Management Plan Version 02.
4		Peripheral neuropathy was removed as "important potential risk" and added as "important identified risk".	Changed from "important potential risk" to "important identified risk"
4		Prolongation of QT interval	Important identified risk "Prolongation of QT interval" covers important identified risk "Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions" and missing information "Usage together with QTc-prolonging drugs or in patients with concurrent risk factors for QTc prolongation"
4		Muscle rupture, ligament rupture were added as "important potential risks"	During the PSUR Work Sharing Procedure (DE/H/PSUR/0023/001 and DE/H/PSUR/0023/002) European Health Authorities requested to include both topics in the EU-RMP as an "important potential risk".

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4		Hypersensitivity and anaphylaxis; hepatotoxicity; renal failure; serious vision disorders; serious bullous skin reactions; depression, suicidality, and psychosis; serious haematological disorders; exacerbation of myasthenia gravis.	Change from “Cumulative case presentation in PSURs” to “Cumulative case presentation in PBRERs/PSURs when new safety relevant information becomes available” in the Pharmacovigilance Plan.
4		Retinal detachment was added as an “important potential risk”	During the Renewal of Marketing Authorisation Procedure (DE/H/ 155+156+158/002/R/003) European Health Authorities requested to include retinal detachment in the EU-RMP as an important potential risk.