VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Moxifloxacin is indicated for treatment of bacterial infection associated with the following conditions:

- Acute Bacterial Sinusitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Pelvic inflammatory disease
- Infections of skin and skin structure

Acute Bacterial Sinusitis: Acute Bacterial Sinusitis is a common condition affecting approximately 12.5% of the population at some point in time. It is an inflammation (redness and soreness) of the nose and cavity surrounding the nose in the skull. It causes headaches, pain and tenderness of the face over the affected area, loss of smell and also being associated with nasal discharge. It can complicate common colds and flu-like illnesses, in 2% of cases in adults and up to 10% of cases in children. Rare complications if left untreated include infection spread to the facial bones and to the brain because of the closeness of the brain tissues. Risk factors include pre-existing allergies and abnormalities of the nasal passages (e.g. deviated septum).

Acute exacerbations of chronic bronchitis: Chronic bronchitis is one of the most common respiratory tract disorders, affecting between 3 and 17% of the population in developed countries. It is an inflammation of the airways, associated with a mucus producing cough (present for at least three months a year in consecutive years), wheezing and variable degrees of difficulty in exercising and breathing. An acute exacerbation is a sudden worsening of symptoms and on average affects patients with chronic bronchitis approximately twice a year.

Community acquired pneumonia (CAP): CAP is a common illness in all parts of the world, affecting between 1.6 and 11.6 in 1,000 people per year. It is an inflammation of the lungs which has not been acquired in a hospital or long-term care institution setting. It is a major cause of death among all age groups, with 6 to 14% of cases which result in hospitalisation resulting in death. Mortality decreases with age until late adulthood; elderly individuals are particularly at risk for CAP and associated mortality. More cases of CAP occur during winter months than during other times of the year. Individuals with underlying illnesses such as Alzheimer's disease, cystic fibrosis, emphysema, tobacco smoking, alcoholism, or immune system problems are at increased risk for pneumonia.

Pelvic inflammatory disease (PID): PID is a common condition affecting women caused by bacterial infections of the reproductive organs. In the United States, more than 750,000 women are affected each year, being most common in teenagers and first-time mothers. Whilst 4 to 6 out of 10 cases are caused by sexually transmitted disease (e.g. gonorrhoea), it can also be caused by bacteria normally found in the vagina. PID may cause infertility in approximately 12.5% of cases, due to damage to the uterine tubes. Other complications include chronic pain and ectopic pregnancy.

Complicated skin and skin structure infections (CSSIs): Skin infections are the most common type of bacterial infection, although the exact prevalence of these amongst the population is unknown. Skin infections classified as complicated include infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, diabetic foot infections, major abscesses, bite wound infections, post-traumatic wound infections and infection of the dead deep layer of the skin. These can range in severity, from mild inflammation to extensive skin tissue damage (resulting in amputation if untreated) and life-threatening sepsis.

VI.2.2 Summary of treatment benefits

Moxifloxacin 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. Moxifloxacin is taken only once daily and is suitable for single-drug antibiotic treatment.

In several clinical trials and numerous published literatures, Moxifloxacin 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 Moxifloxacin therapy in AECB under real-life conditions. In patients with AECBs, cure rates from the bacterial infection or improvement with Moxifloxacin 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 Moxifloxacin ranged from 86% to 96.7%. In the TOPAS studies, a total of 7,090 patients were treated with Moxifloxacin 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, Moxifloxacin showed cure rates, ranging from 83% to 93%. The early onset of the clinical response seen with Moxifloxacin 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 Moxifloxacin under daily-life conditions in patients with cSSSIs. Moxifloxacin 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, Moxifloxacin 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).

VI.2.3 Unknowns relating to treatment benefits

Studies conducted to date have investigated treatment of the above-mentioned indications in male and female patients of a variety of ethnicities over the age of 18 (including elderly patients over the age of 65). There have been no results which suggest reduced clinical cure rates in patients of a particular age, race or gender. However, moxifloxacin effectiveness and safety have not been investigated in children and adolescents due to studies in juvenile animals which have shown damage caused to the cartilage. Therefore, moxifloxacin should not be given to patients under the age of 18.

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.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions (Hypersensitivity, anaphylaxis)	Allergic reactions have been reported with moxifloxacin and similar antibiotics after first administration. These reactions can progress to a life-threatening shock, even after the first administration.	Unpredictable reaction, so cannot be prevented other than by avoidance in patients with known allergy. Moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.
Serious abnormalities of heart rhythm (QTc prolongation)	Animal and human studies show that moxifloxacin has effects on the electrical system of the heart producing changes which can lead to dangerous abnormalities of heart rhythm. Women and elderly patients may be more susceptible to	Use with caution in the patients at greatest risk, i.e. patients with existing forms of heart rhythm disorders, patients with abnormally low blood potassium, patients with very slow heart rates and patients with heart failure

Risk	What is known	Preventability
	these effects.	Avoid use in patients being simultaneously treated with drugs that have similar effects on heart rhythm.
Fits/ convulsions (Seizure)	Antibiotics similar to moxifloxacin (quinolones and fluoroquinolones) are known to trigger fits, particularly in patients with epilepsy. Fits have been reported rarely with moxifloxacin.	Use should be with caution in patients with brain disorders including epilepsy or in the presence of other risk factors which may make fits more common.
Damage to sinews (tendons) including tendon rupture (Tendinopathy)	Disorders of tendons (sinews) which attach muscles to bones have been reported with moxifloxacin and similar antibiotics; occasionally this is associated with the tendon tearing. This risk is more common in the elderly and in patients treated simultaneously with steroid medications. Symptoms can occur up to several months after completing treatment.	Moxifloxacin should not be given to patients with a previous history of tendon problems related to treatment with quinolone antibiotics.
Serious liver damage (Hepatotoxicity)	Mild abnormalities of liver function have been reported commonly; however, cases of serious liver damage, sometimes leading to potential liver failure and death, have also been reported very rarely with moxifloxacin.	Liver function monitoring tests should be performed in cases where there are suspicions of a poorly functioning liver. Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms such as rapidly developing feeling of being unwell associated with yellowing of the skin/eyes (jaundice), dark urine, abnormal bleeding or changes in consciousness occur.
Serious diarrhoea and intestinal inflammation (Antibiotic associated diarrhoea (including colitis))	Antibiotic-associated diarrhoea and intestinal inflammation has been reported in association with the use of many antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis (inflammation of the colon).	No preventative measures known.

Risk	What is known	Preventability
Failed kidney function (Renal failure)	Decreased kidney function and kidney failure have been reported rarely with moxifloxacin. Predisposing factors for developing renal failure during therapy are older age, pre-existing kidney disorders, administration of other medications which may impair kidney function and reduced patient hydration.	Elderly patients with kidney disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of kidney failure.
Serious vision disorders	Visual disturbance such as blurred vision and double vision have been reported uncommonly with moxifloxacin. Temporary loss of vision has been reported very rarely.	No factors are known to prevent serious vision disorders.
Serious skin reactions with blistering (bullous skin reactions)	Serious skin reactions with blistering such as "Stevens-Johnson syndrome" and "toxic epidermal necrolysis", which may potentially be fatal, have been reported very rarely.	Unpredictable reaction, so cannot be prevented other than by avoidance in patients with known sensitivity. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur. Moxifloxacin should be discontinued and suitable treatment initiated.
Depression, thoughts and tendency to commit suicide, and abnormal thinking/ hallucinations (psychosis)	Psychiatric reactions may occur even after the first administration of moxifloxacin and similar antibiotics. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injury such as suicide attempts.	No preventative measures known.
Serious blood disorders (Serious haematological disorders)	Low counts of red and white blood cells as well as the blood cells needed for blood clotting have been reported uncommonly with moxifloxacin, as has an increase in a type of white blood cell called	No preventative measures known.

Risk	What is known	Preventability
	eosinophils. Very rarely, increased blood clotting and a significant decrease of special white blood cells (agranulocytosis) have been reported.	
Worsening of muscle weakness in patients with myasthenia gravis	Moxifloxacin has been very rarely reported to worsen symptoms in patients with myasthenia gravis, a neurological condition associated with profound muscle weakness.	Moxifloxacin should be used with caution in patients with myasthenia gravis.
Damage to the nerves in hands and feet with weakness and/or tingling or "pins and needles" (peripheral neuropathy)	Cases of nerve damage been reported rarely in patients receiving moxifloxacin and other similar antibiotics.	Patients under treatment with moxifloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of nerve damage such as pain, burning, tingling, numbness, or weakness develop.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Muscle destruction, inflammation and weakness (Rhabdomyolysis, myositis and myopathy)	There have been very rare cases of muscle destruction (rhabdomyolysis) reported following treatment with antibiotics similar to moxifloxacin and which might possibly also occur during treatment with moxifloxacin.
Infections due to bacteria resistant to moxifloxacin (Selection of drug-resistant isolates)	All antibiotics have the risk of bacteria developing an acquired resistance. This resistance varies by species and often differs geographically.
A slow heart rate (bradycardia)	Decreased heart rate has been observed in animal studies. To date, moxifloxacin has not been associated with slow heart rate in humans; however, it should not be taken by patients with an existing slow heart rate, whether naturally occurring or caused by other medications.
Muscle rupture	Muscle injury, including rupture, has been observed in use of antibiotics from the same family as moxifloxacin and therefore occurrence cannot be ruled out during moxifloxacin use.
Ligament rupture	Antibiotics from the same family as moxifloxacin are suspected of

Risk	What is known (Including reason why it is considered a potential risk)
	causing ligament rupture and therefore occurrence cannot be ruled out during moxifloxacin use.
Detachment of the retina (Retinal detachment)	Antibiotics from the same family as moxifloxacin are suspected of causing retinal detachment and therefore incidence cannot be ruled out during moxifloxacin use.

Missing information

Risk	What is known
Usage of moxifloxacin in children and growing adolescents	The beneficial effects and safety of moxifloxacin in children and adolescents have not been established.
Joint disease and pain in young patients (Arthropathy (in paediatric patients))	In animal studies, moxifloxacin as with other similar antibiotics has adverse effects on the joints (cartilage). It is not known if the adverse effects seen in animals would also be seen in young patients as joint pain.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan

Not applicable for this generic

List of studies in post authorisation development plan

Not applicable for this generic

Studies which are a condition of the marketing authorisation

Not applicable for this generic

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Not applicable			