VI.B.2 Elements for a public summary

VI.B.2.1 Overview of disease epidemiology

[Moxifloxacin] 400mg/250ml solution for infusion
Moxifloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action.

[Moxifloxacin] solution for infusion is indicated for the treatment of:

- Community acquired pneumonia (CAP)
- Complicated skin and skin structure infections (cSSSI)

Moxifloxacin initial treatment may be followed by oral administration with [Moxifloxacin] tablets when clinically indicated.
After cardiovascular disease, respiratory diseases rank second in terms of mortality, incidence, prevalence, and costs. The European prevalence of chronic obstructive pulmonary disease (COPD) ranges from <2% in France and the UK, to 9% in Spain. Moreover, a Europeanwide increase in the prevalence and mortality of COPD and other smoking-related diseases, particularly in women, is projected for the coming decades. Chronic bronchitis (CB), a component of COPD, usually associated with frequent exacerbations, is even more prevalent; as an example, 4.1% of the French population aged 25+ years develop this disease. Nonetheless, the prevalence of CB differs between countries. In a recent study of young European adults, the prevalence of CB in subjects aged 20–44 years ranged from 0.7% in the UK to 9.7% in Spain, with the prevalence being directly associated with smoking prevalence.

Skin and skin-structure infections (SSSIs) are defined as infections of the epidermis, dermis or subcutaneous tissue. They represent one of the most common indications for antibiotic therapy and account for approximately 10% of hospital admissions in the USA. Direct infection of the skin occurs by invasion of the epidermis, usually after damage to the skin, and infection may affect any anatomical layer.

VI.B.2.2 Summary of treatment benefits

[Moxifloxacin] solution for infusion contains the active substance moxifloxacin, which belongs to a group of antibiotics called fluoroquinolones. [Moxifloxacin] solution for infusion works by killing bacteria that cause infections if they are caused by bacteria that are susceptible to moxifloxacin.
[Moxifloxacin] solution for infusion is used in adults for treating the following bacterial infections:
- Infection of the lungs (pneumonia) acquired outside the hospital
- Infections of the skin and soft tissue

The difference between the infusion and the oral formulation of moxifloxacin preparations is that at the end of the infusion higher concentrations of moxifloxacin are achieved in a shorter period of time. Practically infusion formulation acts faster.

[Moxifloxacin] solution for infusion is for intravenous use and will always be given by a doctor or healthcare professional, who should ensure that the infusion is given at a constant flow over 60 minutes.

Doctor will decide on the duration of treatment with [Moxifloxacin] solution for infusion. In some cases doctor may start treatment with [Moxifloxacin] solution for infusion and then continue treatment with [Moxifloxacin] tablets that work the same way.

The duration of treatment depends upon the type of infection, and how well patient respond to treatment. However, the recommended durations of use are:

- Infection of the lungs (pneumonia) acquired outside the hospital: 7 - 14 days

Most patients with pneumonia were switched to oral treatment with [Moxifloxacin] tablets within 4 days.

- Infections of the skin and soft tissue: 7 - 21 days

For patients with complicated skin and skin structure infections the mean duration of intravenous treatment was approximately 6 days and the average overall duration of treatment (infusion followed by tablets) was 13 days.

The benefit risk balance of moxifloxacin containing medicinal products in intravenous formulations in the approved indications is favorable.

Serious safety concerns such as severe liver disorders, abnormal heart rhythms, severe diarrhea and severe skin reactions will be specifically followed up by questionnaire if they occur during treatment with moxifloxacin.

VI.B.2.3 Unknowns relating to treatment benefits

The treatment benefits remain unknown for children and growing adolescents.

VI.B.2.4 Summary of safety concerns

Important identified risks

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
If you experience allergic reactions, severe sudden allergic reaction *(Hypersensitivity, anaphylaxis)*	In rare cases a severe, sudden allergic reaction (an anaphylactic reaction/shock) even with the first dose can be experienced following [Moxifloxacin] treatment. Symptoms include tightness in the chest, feeling dizzy, feeling sick or faint, or dizziness when standing up.	Yes, by discontinuation of the treatment and immediate consultation of a doctor.
Abnormal ECG changes, delayed conduction of	[Moxifloxacin] can change heart's ECG, especially in	Yes. Drug should not be administered in patients born

electrical signals *(Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions)*	female and elderly. Severe fast heart rhythm is an adverse effect that may affect up to 1 in 100 people using [Moxifloxacin] solution for infusion. The risk of heart problems may increase with increase of the dose and the speed of the perfusion into the vein.	or with any condition with abnormal heart rhythm. Drug should not be administered in patient with salt imbalance in the blood (especially low levels of potassium or magnesium in the blood) or in patients with weak heart. In case that patient takes any medicine that decreases blood potassium level, doctor should be consulted before [Moxifloxacin] administration. As risk of heart problems may increase with increase of the dose, recommended dosage of [Moxifloxacin] should be followed. Monitoring of heart rhythm by ECG measure may be recommended during treatment.
Quinolone antibiotics, including [Moxifloxacin], may cause convulsions *(Seizure)*	[Moxifloxacin], as quinolones does, can activate CNR problems in patient suffering from epilepsy or conditions makes likely to have convulsions	Yes, by drug discontinuation and treatment with appropriate drugs if needed.
Tendon inflammation, tendon rupture *(Tendinopathy)*	[Moxifloxacin] may cause pain and inflammation of tendons, even within 48 hours of starting treatment and up to several months after discontinuing [Moxifloxacin] therapy. The risk of inflammation and rupture of tendons is increased in elderly or in patients taking corticosteroids. [Moxifloxacin], should not be administerd if patient	Yes, by immediate drug discontinuation of the treatment. At the first sign of any pain or inflammation [Moxifloxacin] treatment should be stopped and patient should rest the affected limb(s). Avoid any unnecessary exercise, as this might increase the risk of a tendon rupture

	experienced previously problem with tendons related to quinolone antibiotics treatment.	
Severe liver disorders *(Hepatotoxicity)*	[Moxifloxacin] should not be administered in patient with severe liver disease or increased liver enzymes (transaminases) higher than 5 times the upper normal limit. Increase of a special liver enzyme in the blood (gamma-glutamyl-transferase) is an adverse effect that my affect up to 1 in 10 people using [Moxifloxacin] solution for infusion. Therefore, [Moxifloxacin] may cause a rapid and severe inflammation of the liver which could lead to life-threatening liver failure.	Yes, by discontinuation of the treatment. Doctor should be advised if patient suddenly feel unwell and/or are being sick and also if has yellowing of the whites of the eyes, dark urine, itching of the skin, a tendency to bleed or disturbances of thought or wakefulness.
Diarrhea (including Severe diarrhea, containing blood and/or mucus) *(Antibiotic associated diarrhea (including colitis) in hospital setting)*	Diarrhea can be developed whilst or after taking antibiotics including [Moxifloxacin]. Severe diarrhea, containing blood and/or mucus is an adverse event that may affect up to 1 in 100 people using [Moxifloxacin] solution for infusion	Yes, by discontinuation of the treatment if diarrhea becomes severe or persistent or if stool contains blood or mucus. [Moxifloxacin] should not be administered with medicines that stop or slow down bowel movement.
Kidney problems *(Renal failure)*	[Moxifloxacin] should be used with caution in elderly persons with renal disorders if they are unable to maintain adequate fluid intake. Kidney impairment (including increase in special kidney laboratory test results like urea and creatinine), kidney failure, are adverse event that may	Yes, if drink plenty whilst taking [Moxifloxacin]

	affect up to 1 in 100 people using [Moxifloxacin] solution for infusion	
Problems with vision *(Serious vision disorders)*	[Moxifloxacin] may cause double or blurred vision. Sudden, transient loss of vision may also be occurred.	Yes, by consulting immediately an eye specialist in case that patient's eyesight becomes impaired
If you develop a skin reaction or blistering / peeling of the skin and/or mucosal reactions *(Serious bullous skin reactions)*	[Moxifloxacin] is associated with a risk of potentially life threatening bullous skin reactions like Stevens-Johnson-Syndrome (SJS) or toxic epidermal necrolysis (TEN).	Yes, by contacting your doctor immediately before you continue treatment.
Depression, suicidal thoughts, mental health problems *(Depression, suicidality, and psychosis)*	Quinolone antibiotics, including [Moxifloxacin], can cause mental health problems, when administered for the first time. In very rare cases depression or mental health problems have led to suicidal thoughts and self-endangering behaviour such as suicide attempts.	Yes, by discontinuation of the drug
Aneamia, low white blood cell count, low numbers of special white blood cells, decrease or increase of special blood cells necessary for blood clotting, increased specialised white blood cells, decreased blood clotting *(Serious haematological disorders)*	Low red blood cell count, low white blood cells count, low numbers of special white blood cells (neutrophils), decrease or increase of special blood cells necessary for blood clotting, increased specialised white blood cells (eosinophils), decreased blood clotting are adverse events been experienced in a frequency of up to 1 in 100 people	Yes. In case that patient takes medicines to thin his blood (oral anticoagulants such as warfarin), more frequently monitoring of the INR may be requested. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.
Abnormal muscle fatigue leading to weakness and in serious cases paralysis *(Exacerbation of myasthenia gravis)*	In patients already suffering from abnormal muscle fatigue taking [Moxifloxacin] may worsen the symptoms of the disease.	Yes, by immediate consulting of the doctor

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Very slow heart rhythm *(Bradycardia)*	Moxifloxacin should be used with caution in patients with heart rhythms problems because can cause changes in the ECG. In addition, co administration of [Moxifloxacin] with other medicines that can lower blood potassium levels (e.g. some diuretics, some laxatives and enemas [high doses] or corticosteroids [anti-inflammatory drugs], amphotericin B) or cause a slow heart rate can also increase the risk of serious heart rhythm disturbances.
Muscle reactions with muscle cell damage *(Rhabdomyolysis, myositis, and myopathy)*	This adverse event is been reported following treatment with other quinolone antibiotics, but might possibly also occur during treatment with [Moxifloxacin] in very rare cases
Troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities *(Peripheral neuropathy)*	In rare cases troubles associated with the nervous system such as pain, burning, tingling, numbness and/or weakness in extremities have been reported. Therefore, doctor should be immediately inform about these symptoms in aim to decide on the discontinuation or not of the treatment
Bacteria against [Moxifloxacin] is active *(Selection of drug resistant isolates)*	[Moxifloxacin] is used in adults for treating the following bacterial infections: - Infection of the lungs (pneumonia) acquired outside the hospital - Infections of the skin and soft tissue. [Moxifloxacin] should be given intravenously (in the vein) only, and should not be administered into an artery. There is limited experience on use of sequential intravenous/oral [Moxifloxacin] for the treatment of infection of the lungs (pneumonia) acquired outside the hospital.

Important missing information

Risk	What is known
Moxifloxacin usage together with QTc-prolonging drugs or in patients with concurrent risk factors for QTc prolongation	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: - anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide) - anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) - neuroleptics (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).
Use of moxifloxacin in children and growing adolescents	Moxifloxacin is contraindicated in children and growing adolescents. Efficacy and safety of moxifloxacin in children and adolescents have not been established
Arthropathy (in paediatric patients)	Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals.

VI.B.2.5 Summary of risk minimisation measures by safety concern

Safety concern	Additional risk minimization measures
Hypersensitivity, anaphylaxis	None proposed
Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions	None proposed
Seizure	None proposed
Tendinopathy	None proposed
Hepatotoxicity	None proposed
Antibiotic associated diarrhea (including colitis) in hospital setting	None proposed

Renal failure	None proposed
Serious vision disorders	None proposed
Serious bullous skin reactions	None proposed
Depression, suicidality, and psychosis	None proposed
Serious haematological disorders	None proposed
Exacerbation of myasthenia gravis	None proposed
Bradycardia	None proposed
Rhabdomyolysis, myositis, and myopathy	None proposed
Peripheral neuropathy	None proposed
Selection of drug resistant isolates	None proposed
Moxifloxacin usage together with QTc-prolonging drugs or in patients with concurrent risk factors for QTc prolongation	None proposed
Use of moxifloxacin in children and growing adolescents	None proposed
Arthropathy (in paediatric patients)	None proposed

VI.B.2.6 Planned post authorisation development plan

Not applicable

VI.B.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	31.05.2013	NA	Initial version
2.0	02.10.2013	NA	Day 160 – Deficiency Letter answers