Part VI: Summary of the risk management plan

Summary of risk management plan for Levofloxacin 5 mg/mL Solution for infusion (levofloxacin)

This is a summary of the risk management plan (RMP) for Levofloxacin 5 mg/mL Solution for infusion (hereinafter referred to as LEVOFLOXACIN). The RMP details important risks of LEVOFLOXACIN, how these risks can be minimised, and how more information will be obtained about LEVOFLOXACIN's risks and uncertainties (missing information).

LEVOFLOXACIN's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LEVOFLOXACIN should be used.

Important new concerns or changes to the current ones will be included in updates of LEVOFLOXACIN's RMP.

I. The medicine and what it is used for

LEVOFLOXACIN is authorised in adults for the treatment of the following infections:

• Community-acquired pneumonia

• Complicated skin and soft tissue infections

For the above-mentioned infections LEVOFLOXACIN should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis and complicated urinary tract infections

• Chronic bacterial prostatitis

• Inhalation Anthrax: post exposure prophylaxis and curative treatment.

(see SmPC for the full indication).

It contains levofloxacin (as hemihydrate) as the active substance, and it is given by slow intravenous infusion.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of LEVOFLOXACIN together with measures to minimise such risks and the proposed studies for learning more about LEVOFLOXACIN's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of LEVOFLOXACIN, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of LEVOFLOXACIN are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LEVOFLOXACIN. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Aortic aneurysm and dissection • Disabling, long-lasting and potentially irreversible side effects • Heart valve regurgitation/incompetence
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important identified risk: Aortic aneurysm and dissection	
Risk minimisation measures	Routine Risk minimisation measures: SmPC sections: 4.4, 4.8 Recommendation to use fluoroquinolones only after a 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, advice for immediate consult by a physician in an emergency department in case the patient experiences sudden abdominal, chest or back pain are included in SmPC section 4.4. PL sections: 2, 4 Communication with the doctor before taking this medicine in case the patient has been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm), has experienced a previous episode of aortic dissection or has a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions are included in PL section 2. Recommendation to reach immediately an emergency room in case the patient feels sudden, severe pain in abdomen, chest or back, especially if there is treatment with systemic corticosteroids is included in PL section 2. Legal status: Prescription only medicine Additional risk minimisation measures: DHPC

Important identified risk: Disabling, long-lasting and potentially irreversible side effects	
Risk minimisation measures	Routine Risk minimisation measures: SmPC sections: 4.1, 4.3, 4.4, 4.8 Use of levofloxacin only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of the indicated infections is included in SmPC section 4.1. Contraindication of use in patients with a history of tendon disorders related to fluoroquinolone administration is included in SmPC section 4.3. Avoiding use in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products and initiation of their treatment with levofloxacin only in the absence of alternative treatment options and after careful benefit/risk assessment

	is included in SmPC section 4.4. Avoiding concomitant use of corticosteroids and in case signs of tendinopathy occur, discontinuation of treatment at the first sign of tendinitis, consideration of alternative treatment and appropriate treatment of the affected limb(s) are included in SmPC section 4.4. Discontinuation of levofloxacin in case psychotic reactions develop and institution of appropriate measures, alongside caution in psychotic patients or in patients with history of psychiatric disease is included in SmPC section 4.4. Communication with the physician prior to continuing treatment if symptoms of neuropathy develop in order to prevent the development of potentially irreversible condition is included in SmPC section 4.4. Caution in use in patients with a known history of myasthenia gravis because of exacerbation of muscle weakness is included in SmPC section 4.4. Consultation with an eye specialist immediately in case vision becomes impaired or any effects on the eyes are experienced is included in SmPC section 4.4. Immediate discontinuation of treatment at the first signs or symptoms of any serious adverse reaction and communication with the prescriber for advice is included in SmPC section 4.4. PL sections: 2, 4 Contraindication of use in case the patient has previously had problems with their tendons, such as tendonitis, related to treatment with a quinolone antibiotic is included in PL section 2. Contraindication of use and communication with the doctor as soon as possible before taking levofloxacin if the patient has experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone is included in PL section 2. Communication with the doctor before taking levofloxacin if the patient is 60 years of age or

	older is included in PL section 2. Communication with the doctor before taking levofloxacin if the patient has kidney problems is included in PL section 2. Communication with the doctor before taking levofloxacin if the patient uses corticosteroids is included in PL section 2. Discontinuation of treatment and immediate communication with the doctor at the first sign of any tendon pain or inflammation, rest of the painful area and avoiding any unnecessary exercise, are included in PL section 2. Discontinuation of treatment and communication with the doctor in case the patient experiences symptoms of nerve damage (neuropathy) such as as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms are included in PL section 2. Immediate communication with an eye specialist if the eyesight becomes impaired or if the eyes seem to be otherwise affected is included in PL section 2. Communication with the doctor prior to continuing treatment with levofloxacin in order to decide either on continuing treatment or considering an antibiotic from other class, in case the patient experiences any serious side effects is included in PL section 2. Discontinuation of treatment and communication with the physician immediately as there may be the need for urgent medical advice in case the patient notices pain and inflammation in tendons or ligaments, fits (convulsions), pain, burning, tingling or numbness during treatment with levofloxacin are included in PL section 4. Immediate communication with an eye specialist if the patient notices vision impairment or any other eye disturbances while taking levofloxacin, is included in PL section 4. Legal status: Prescription only medicine Additional risk minimisation measures:

	DHPC

Important identified risk: Heart valve regurgitation/incompetence	
Evidence for linking the risk to the medicine	The study by Etminan et al. 2019 investigates whether oral fluoroquinolones increase the risk of aortic and mitral backflow (regurgitation). To address this question, data from the U.S. Food and Drug Administration's adverse reporting system (FAERS) database was used to undertake a disproportionality analysis, and a random sample of 9,053,240 patients from the U.S. PharMetrics Plus database (IQVIA) was used for the matched nested case-control study (NCC). The results from the disproportionality analysis identified a total of 102 fluoroquinolone-related valvular backflow (regurgitation) cases between 2004 to 2018 from FAERS. The combined reporting odds ratio (ROR) was 1.45 (95% CI: 1.20-1.77), whereas the individual RORs were 1.67 (95% CI: 1.24-2.25) for ciprofloxacin, 2.87 (95% CI: 1.29-6.39) for gatifloxacin, 1.80 (95% CI: 1.37-2.37) for levofloxacin, and 0.73 (95% CI: 0.41-1.32) for moxifloxacin. It should be noted that gatifloxacin is no longer marketed, neither in the EU (since 2004) nor the U.S (since 2008). In a disproportionality analysis a value of >1 signals increased risk. In conclusion, initial analyses of spontaneous reports in the FAERS database showed an increased risk of valvular backflow (regurgitation) after fluoroquinolone exposure compared to all other drugs. The NCC study was conducted with data from 2006 to 2016 using the U.S. PharMetrics Plus database (IQVIA), which is a commercial data source of health insurance. The initial group (cohort) included 9,053,240 patients. Conditions for which fluoroquinolones can be prescribed and that can independently increase the risk of valvular backflow (regurgitation) were excluded prior to the identification of cases and control subjects resulting in a study group (cohort) of 8,272,981 patients. Within the NCC study group (cohort), the authors identified 12,502 cases of valvulopathy and 125,020 controls. The study analysed three distinct exposure periods, i.e. current, recent and past use of fluoroquinolones. Current fluoroquinolone exposure implied an active prescription at the index date or 30 days prior to the event date. Recent fluoroquinolone exposure was defined as fluoroquinolone use within days 31 to 60 and past exposure within days 61 to 365 prior to the event date. Amoxicillin and azithromycin served as active comparators, as their indications overlap with those of fluoroquinolones. The adjusted RRs for current users of fluoroquinolone compared with amoxicillin and azithromycin users were 2.40 (95% CI: 1.82 to 3.16) and 1.75 (95% CI:1.34 to 2.29), respectively. The adjusted RRs for recent and past fluoroquinolone users when compared with amoxicillin were 1.47 (95% CI: 1.03 to 2.09) and 1.06 (95% CI: 0.91 to 1.21), respectively. Based on the results, it was concluded that the risk of mitral and aortic regurgitation is doubled for current users of fluoroquinolones and declines via recent to past users. It can be thus deducted that the risks for fluoroquinolone-related valvular backflow (regurgitation) are highest in the first 30 days after drug intake, but elevated risk levels can still be observed up to 2 months after fluoroquinolone exposure — even though risks for recent users

	are smaller. Past fluoroquinolone exposure, on the other hand, shows only very low risk estimates. For current user, higher risk estimates were observed under fluoroquinolone exposure in comparison with amoxicillin than in comparison with azithromycin. Finally, a sensitivity analysis based on the metric E-value concluded that an unmeasured confounder would have to be linked to the outcome (aortic and mitral backflow) and the exposure with an association equal to at least 4.2 (95% CI: 3.0 to 5.8) to eliminate the observed risk seen with current users of fluoroquinolones. For recent and past use periods, no sensitivity outcomes were reported. However, future studies are necessary to confirm or refute these associations. In a non-clinical study (Guzzardi et al., 2019) human aortic myofibroblasts were isolated from 9 patients with aortopathy undergoing elective ascending aortic removal (resection). The capacity for extracellular matrix degradation in cells exposed to fluoroquinolone was assessed by multiplex analysis of secreted matrix metalloproteinases (MMPs) relative to tissue inhibitors of MMPs. Direct evaluation of extracellular matrix degradation was investigated in human aortic cells using a 3-dimensional gelatin-fluorescein isothiocyanate fluorescence microgel assay. The in vitro data indicated that ciprofloxacin alters MMPs/tissue inhibitor of MMP ratios leading to increased MMP protease activity and in consequence to maladaptive cell-mediated collagen fiber degeneration. In addition to the deranged MMPs/tissue inhibitor of MMP ratios, collagen-1 expression in human aortic myofibroblasts, responsible for biomechanical stability of the aortic tissues, was significantly decreased after high dose administration of ciprofloxacin. This was, detected in protein expression experiments using immunoblotting and immunofluorescent staining. These novel data may provide a cellular and molecular mechanism to explain the established clinical association between fluoroquinolone exposure and acute aortic events. Furthermore, a search in EudraVigilance Data Analysis System (EVDAS) through 08-Oct-2019 for cardiac valve disorders associated with fluoroquinolones for systemic use revealed 11 cases where some patients experienced in addition to the valvular backflow (regurgitation) a musculoskeletal or connective tissue disorders. Since these events were experienced simultaneously, a common pathomechanism for the events can be expected.
Risk factors and risk groups	Aortic backflow (regurgitation)and mitral backflow (regurgitation)result from dysfunction or altered anatomy of aortic or mitral valve leaflets, their supporting structures, or both. Aortic causes of aortic regurgitation include annuloaortic distension (ectasia) (idiopathic root dilatation, Marfan syndrome, aortic dissection, collagen vascular disease, and syphilis). Mitral regurgitation is roughly classified as organic (primary) or functional (secondary). Causes of primary mitral regurgitation include most commonly degenerative disease (Barlow, fibroelastic degeneration, Marfan syndrome, Ehler's-Danlos syndrome, annular calcification), rheumatic disease, and endocarditis. Ruptured papillary muscle secondary to myocardial infarction defined an organic ischaemic mitral regurgitation. Causes of secondary mitral regurgitation include ischaemic heart disease and cardiomyopathy. Observed population at higher risk of heart valve backflow (regurgitation) are patients with congenital heart valve disease, patients with connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, high blood pressure (hypertension),

	Turner's syndrome, Behcet's disease, rheumatoid arthritis, and infective endocarditis.
Risk minimization measures	Routine risk minimization measures SmPC sections: 4.4, 4.8 Recommendation to use fluoroquinolones only after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of congenital heart valve disease, or in patients diagnosed with pre-existing heart valve disease, or in presence of other risk factors or conditions predisposing for heart valve regurgitation/incompetence and seek of immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities are included in SmPC section 4.4. PL sections: 2, 4 Communication with the doctor before taking this medicine in case the patient has been diagnosed with leaking heart valves (heart valve regurgitation) or has a family history of congenital heart valve disease, or other risk factors or predisposing conditions is included in PL section 2. Communication with the doctor in case the patient starts experiencing a rapid onset of shortness of breath, especially when lying down flat in bed, or notices swelling of ankles, feet or abdomen or a new onset of heart palpitations is included in PL section 2. Legal status: Prescription only medicine Additional risk minimisation measures: DHPC

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of LEVOFLOXACIN.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for LEVOFLOXACIN.