Swiss Risk Management Plan Summary

QUOFENIX® (Delafloxacin)

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Marketing authorization holder: A. Menarini GmbH, Switzerland
Quofenix® tablets / Quofenix® powder for concentrate for solution for infusion

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Quofenix is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Quofenix in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. A. Menarini Gmb is fully responsible for the accuracy and correctness of the content of the published summary RMP of Quofenix.

SUMMARY OF RISK MANAGEMENT PLAN FOR QUOFENIX (DELAFLOXACIN)

I. THE MEDICINE AND WHAT IT IS USED FOR

Quofenix is authorised for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see SmPC for the full indication). It contains delafloxacin as the active substance and it is given by oral (450 mg tablets) or intravenous infusion (300 mg of powder for concentrate for solution for infusion) administration.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Quofenix, together with measures to minimise such risks and the proposed studies for learning more about Quofenix'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 Quofenix, 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, including PSUR assessment 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 Quofenix are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered or taken. 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 Quofenix. 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	• Tendinopathy • Peripheral Neuropathy • Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection
Important Potential Risks	• Long-lasting and / or potentially irreversible severe adverse reactions • Renal damage secondary to sulfobutylether-β-cyclodextrin (SBECD) accumulation in patients with severe renal impairment [IV formulation]
Missing Information	• None

II.B. Summary of important risks

Important identified risk: Tendons Injuries (Tendinopathy)	
Evidence for linking the risk to the medicine	Fluoroquinolones are associated with an increased risk of inflammation of tendons (tendinitis) and tendon rupture. During delafloxacin clinical development, no tendon rupture was seen.
Risk factors and risk groups	A positive family history is significant solitary risk factor for tendinopathy, increasing the risk fivefold. Risk factors for developing inflammation of the tendons (tendinitis) include age, working in particular jobs that involve repetitive motions, awkward positions, frequent overhead reaching, vibration or forceful exertion or participating in sports that involve repetitive motions.
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.2 Posology and method of administration - SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin You must not be given/Do not take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures No risk minimisation measures

Important identified risk: Damage to the nerves in arms and legs (Peripheral Neuropathy)	
Evidence for linking the risk to the medicine	Systemic fluoroquinolones have been associated with an increased risk of damage to the nerves in arms and legs (peripheral neuropathy). For delafloxacin, during the clinical trials, the incidence of potential peripheral neuropathy was estimated as 0.8%.
Risk factors and risk groups	Damage to the nerves in arms and legs (peripheral neuropathy) can result from traumatic injuries, infections, metabolic problems, inherited causes and exposure to toxins. One of the most common causes is diabetes mellitus (condition in which the patient has high blood sugar levels). In particular, damage to the nerves in arms and legs (peripheral neuropathy) risk factors include: diabetes mellitus; alcohol abuse; vitamin deficiencies, particularly B vitamins; infections, such as Lyme disease, shingles, Epstein-Barr virus, hepatitis C and HIV; immune system disorders, such as Guillian-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, kidney, liver or thyroid disorders; exposure to toxins; repetitive motion and family history of neuropathy.
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions Legal status: prescription only medicine Additional risk minimisation measures No risk minimisation measures

Important identified risk: Enlargement and weakening of the aortic wall or a tear in the aortic wall and of leaking heart valves (Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection)	
Evidence for linking the risk to the medicine	Fluoroquinolones are among the most used antibiotics at world level thanks to their expanded spectrum of action, to excellent bioavailability oral and also for a manageable phenomenon of bacterial resistance. Although generally well tolerated, these drugs can cause rare but serious adverse reactions to when they add also these raw evidence of greater risk of dilatation and aortic rupture. A recent study showed that ciprofloxacin, a fluoroquinolone, increases susceptibility to aortic dilatation and rupture in a mouse model of moderate. Another recent study showed a 66% increase in aortic dilatation and aortic rupture in patients treated with fluoroquinolones compared to amoxicillin. From this study emerges with fluoroquinolones a risk of aorta dilatation contained, but not negligible given the wide use of this class of drugs. The damage mechanism of the aortic wall deserves to be clarified, but it can be hypothesized, in analogy with what is described in tendinopathies and tendon ruptures associated with fluoroquinolones, a damage of the extracellular matrix and in particular of collagen favored by the activation of metalloproteases. An epidemiological study reported an about 2-fold increase in risk of leaking heart valves in patients taking systemic fluoroquinolones compared with patients taking other antibiotics (amoxicillin or azithromycin). A non-clinical study reported that exposure to ciprofloxacin led to a collagen degradation in aortic myofibroblast from patients at higher risk for aortic disorders including aortic regurgitation. Fluoroquinolones as a class are at least possibly causally associated with the occurrence of leaking heart valves. Factors that increase the risk for leaking heart valves include a congenital heart valve disease, connective tissue disorders.
Risk factors and risk groups	The increased risk of aortic aneurysm and dissection is particularly in elderly patients. Risk factors coud be conditions that predispose to dilatation, aortic rupture and leaking heart valves, including a family history or a pre-existing condition of aortic dilatation or aortic rupture, congenital disorders with collagen defects such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis, aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally conditions that predispose for leaking heart valves (e.g. infective endocarditis). The risk may be increased in patients treated with systemic corticosteroids.
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given / take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures - Direct Healthcare Professional Communication (DHPC)

Important potential risk: Long-lasting and / or potentially irreversible severe adverse reactions	
Evidence for linking the risk to the medicine	Some of the serious adverse drug reactions associated with the use of quinolones and fluoroquinolones could very rarely be long-lasting, disabling and potentially irreversible and that these risks are a class effect. Most of the information on the long-lasting, disabling and potentially irreversible character of adverse drug reactions already known for (fluoro)quinolones is available from analysis of spontaneously reported data. Some studies suggest that peripheral neuropathy associated with (fluoro)quinolones use can be severe, debilitating and permanent. (Fluoro)quinolones effects on Central Nervous Sistem are well recognised

	being the second most common reported adverse drug reactions reported in association with these medicinal products. However, data on the long-lasting, disabling and potentially irreversible adverse drug reactions related to the Central Nervous Sistem has not been studied systematically and most of the information from the scientific literature can be found in publications analysing spontaneous data. Considering all available information, there is a reasonable amount of evidence pointing to the causal association between (fluoro)quinolones and long-lasting, disabling and potentially irreversible reactions that manifest as Central Nervous Sistem effects and psychiatric disorders.
Risk factors and risk groups	There is some uncertainty about risk factors related directly to the long-lasting, disabling and potentially irreversible adverse drug reactions. The risk of quinolone-induced tendinopathy can be increased by underlying disease or co-administrated medicines. A review of an article mentioned that predisposing factors for tendinopathy are corticosteroid therapy, advanced age, renal disease, haemodialysis and transplantation. These findings are consistent with an another study that also proposed other risk factors such as rheumatic disease, gout, high doses of quinolones, male gender and age over 60 years.
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures No risk minimisation measures

Important potential risk: Renal damage secondary to sulfobutylether-β-cyclodextrin (SBECD) accumulation in patients with severe renal impairment [IV formulation]	
Evidence for linking the risk to the medicine	Accumulation of the intravenous vehicle (SBECD) can occur in renally impaired patients and it is considered as important potential risk in patients with severe renal impairment which could lead to serious outcomes.
Risk factors and risk groups	Patient with severe renal impairment.
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 3 How to use delafloxacin Legal status: prescription only medicine Additional risk minimisation measures No risk minimisation measures

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 of specific obligation of Quofenix.

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

There are no studies required for Quofenix.