RISK MANAGEMENT PLAN SUMMARY

QUINSAIR 240 mg / 2.4 mL (100 mg/mL) nebuliser solution (levofloxacin hemihydrate)

RMP Version number: 3.1

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Marketing Authorization Holder: Chiesi SA, Villars-sur-Glâne, Switzerland

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 Quinsair 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 Quinsair in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Chiesi SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Quinsair.

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for QUINSAIR (levofloxacin hemihydrate)

This is a summary of the risk management plan (RMP) for QUINSAIR. The RMP details important risks of QUINSAIR, how these risks can be minimized, and how more information will be obtained about QUINSAIR's risks and uncertainties (missing information).

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

This summary of the RMP for QUINSAIR should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

QUINSAIR is authorized for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adult patients with cystic fibrosis (CF) (see SmPC for the full indication). It contains levofloxacin hemihydrate as the active substance and it is given by inhalation twice daily.

Further information about the evaluation of QUINSAIR's benefits can be found in QUINSAIR's EPAR, including its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/quinsair

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

Important risks of QUINSAIR, together with measures to minimise such risks and the proposed studies for learning more about QUINSAIR'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 QUINSAIR these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks below.

In addition to these measures, information regarding adverse reactions is collected continuously and regularly analyzed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of QUINSAIR is not yet available, it is listed under 'missing information' below.

II.A. A List of important risks and missing information

Important risks of QUINSAIR are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered 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 QUINSAIR. 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	• Tendon disorders (including Tendinitis and Tendon Rupture) • Long-lasting, disabling, and potentially irreversible serious reactions
Important potential risks	• Aortic aneurysm/ Aortic dissection • Heart Valve Regurgitation • Off label use in <18 years (especially musculoskeletal effects) • Haemoptysis • Hepatotoxicity • Decreased susceptibility to *P. aeruginosa*
Missing information	• Long-term safety

II.B. Summary of important risks

Important identified risk: Tendon disorders (including Tendinitis and Tendon Rupture)	
Evidence for linking the risk to the medicine	Evidence source: Literature, clinical trials. Strength of evidence: The incidence of FQ-associated tendinopathy or tendon rupture in an otherwise healthy population is estimated to be 0.14% to 0.4%. A study from the UK calculated the excess risk for FQ-associated tendinopathy at 3.2 per 1000 patient years. The incidence of FQ-associated Achilles tendon rupture was estimated as 2.7 per 10,000 patients for ofloxacin and 0.9 per 10,000 patients for ciprofloxacin. Ciprofloxacin was reported to be the most common FQ in 90% of FQ-associated tendon disorders, with the risk of tendinopathy appearing to be dose-dependent [Seeger et al., 2006, Williams, 3rd. et al., 2000], [Kashida and Kato, 1997]. The mean age of patients with FQ-associated tendinopathy is 64 years, with a male-to-female ratio of 2:1, and 27-percent of patients have bilateral involvement [Kim, 2010]. Symptoms of tendinitis may vary from mild aches to local joint stiffness and treatability highly depends on the severity of the events. During clinical trials with MP-376, non-serious events pertaining to the risk have been reported. During MPEX-204, MPEX-2017 and MPEX-209, the incidence rate of tendinitis in the treatment arm was 0.7% (3/409) [95% CI 0.2 to 2.1], which was similar to the placebo group at 0.7% (1/146) [95% CI 0.0 to 3.8]. During the study MPEX-207, there was 1 case of tendinitis assessed as moderate and possibly related in a 24-year-old patient 4 days after starting MP-376. The adverse event lasted for one week, the study drug was discontinued, and the patient recovered. During the study MPEX-209, there was one case of tendinitis in a 26-year-old patient occurring at day 105 during 2nd off-treatment cycle. Tendinitis lasted 5 days and was assessed as moderate and possibly related. The study drug was discontinued. Another patient aged 31-year-old experienced joint stiffness which occurred 1 week after starting the second cycle of MP-376 and resolved after 2 weeks without specific treatment. It was assessed as possibly related to study drug. In MPEX-209 EXT, the incidence rate of tendinitis was 1.1% (1/88) [95% CI 0.0 - 6.2]. A 41-year-old patient experienced tendinitis at Day 224 (day 1 of the 5th on-treatment cycle). The tendinitis lasted 3 months and 3 weeks. It was assessed as moderate and unlikely related to the study drug. The patient received physical therapy and arthroscopy (surgery). In the meantime, this patient also experienced a mild tendon pain, which lasted 15 days and was assessed as non-serious, mild and unlikely related to the study drug.
Risk factors and risk groups	The reported risk factors for FQ-associated tendinopathy and tendon rupture, which is a dose-dependent adverse effect

Important identified risk: Tendon disorders (including Tendinitis and Tendon Rupture)	
	[Kaleagasioglu and Olcay, 2012], [Williams, 3rd. et al., 2000], [Seeger et al., 2006, Kashida and Kato, 1997], include systemic corticosteroid therapy, renal failure, diabetes mellitus, sports activity, history of musculoskeletal disorders and age over 60 years. 41 percent of the reported patients concomitantly used corticosteroids. Some patients had been taking long-term oral corticosteroids. Others had received a corticosteroid injection within the past 3 days. Furthermore, patients older than 60 years were at a 1.5-fold and a 2.7-fold greater risk for development of tendinopathy and tendon rupture, respectively, compared with patients less than 60 years of age. End- stage renal disease was also postulated as a risk factor, since 12% of cases were associated with renal disease alone. Other factors such as obesity, hyperlipidemia and hyperparathyroidism are well known risk factors for tendinopathy or tendon rupture, and their risk potential is possibly exacerbated by concomitant FQ use [Kim, 2010].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3, 4.4., 4.8 • PL section 2 where signs of inflammation of the tendon are provided • PL section 4 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLI-LEVFLAA1-01 See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Long-lasting, disabling, and potentially irreversible serious reactions	
Evidence for linking the risk to the medicine	Evidence source: Literature, FDA boxed warning, EudraVigilance data, PRAR Referral under Article 31 (of Directive 2001/83/EC). Strength of evidence: In 2016, the FDA had finalized a safety review of disabling and potentially permanent serious side effects focusing on cases reporting of AEs from two or more of the following body systems: Musculoskeletal, Senses (vision, hearing, etc.), Neuropsychiatric, Skin, Peripheral Nervous System and Cardiovascular; and lasting 30 days or longer after stopping the FQ referred to as FQ associated Disability. Based on this review, the FDA recommended that for some indications (acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections) the serious side effects outweigh the benefits for the patient and FQs should only be used if no alternative treatment

Important identified risk: Long-lasting, disabling, and potentially irreversible serious reactions	
	options exist. In 2017, data from BfArM national safety database revealed a number of such cases triggering, together with some published literature articles, the Article 31 Referral in the EU.
Risk factors and risk groups	Depending of type of observed ADRs, a wide range of risk factors/ confounders have been mentioned in the scientific literature e.g. corticosteroid therapy, advanced age, and renal disease for tendinopathy [Mandell and Tillotson, 2002]; high dose of FQ, female gender, and pre-existence of central nervous system disease for neurotoxic effects [Tomé and Filipe, 2011, Hedenmalm and Spigset, 1996, Ali, 2014]. FQ-induced mitochondrial dysfunction possibly leading to multifactorial ADRs have not been extensively discussed in scientific literature so far. Golomb et al. mentioned concomitant medication such as chemotherapy, HIV protease inhibitors, statins and amiodarone that can amplify the risk of quinolones mitochondrial toxicity [Golomb et al., 2015], however, these conclusions are limited by the low number of case reports assessed within this study. In summary, risk factors related directly to the long-lasting, disabling and potentially irreversible ADRs remain one of the main uncertainties according to PRAC assessment report published in Oct 2018 [PRAC assessment report 2018].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4, 4.8 • PL section 2 Additional risk minimisation measures: • None

Important potential risk: Aortic aneurysm/ Aortic dissection	
Evidence for linking the risk to the medicine	Evidence source: Non-clinical and epidemiologic studies, PRAC signal validation. Strength of evidence: Data of epidemiologic [Lee et al., 2018, Pasternak et al., 2018b, Daneman et al., 2015, Pasternak et al., 2018b, Pasternak et al., 2018a] and non-clinical studies [LeMaire et al., 2018] had indicated an increased risk of aortic aneurysm and aortic dissection after treatment with FQs as a class leading to PRAC signal evaluation in Sep 2018. The non-clinical study of LeMaire et. al. examined effects of ciprofloxacin on aortic aneurysm and dissection (AAD) development in a mouse model comparing mice challenged with high-fat diet and low-dose angiotensin infusion (1000 ng/min/kg) against a control group of unchallenged mice with normal diet and saline infusion. Aortic challenge itself induced moderate aortic destruction with development of AAD in 17 of 38 (45%)

Important potential risk: Aortic aneurysm/ Aortic dissection	
	mice and severe AAD in 9 (24%) mice, but no rupture or death. Significantly increased incidence of AAD in 38 of 48 (79%) mice, severe AAD in 32 (67%) mice, and rupture and premature death in 7 (15%) were observed in the aortic challenged group treated with ciprofloxacin (100mg/kg/d). As no notable aortic destruction was observed in unchallenged mice that received ciprofloxacin, the authors concluded that ciprofloxacin should be used with caution in patients with aortic dilatation and at high risk of AAD [LeMaire et al., 2018]. The cohort study in Sweden by Pasternak et al. investigated the risk of aortic aneurysm and aortic dissection associated with oral FQ use, as compared with amoxicillin use, within a 60-day period from start of treatment [Pasternak et al., 2018a]. The study addressed some of the confounding factors noted for the two previous studies by Daneman et al. and Lee et al. (e.g., confounding by indication by introducing an active antibiotic treatment arm), who both aimed at exploring any association between collagen-related disorders and FQs. However, the authors also noted that some residual confounding (e.g., risk factors of smoking) may not have been accounted for. It is of note that the risk found in this Swedish cohort is smaller than risk previously reported in other studies. The authors found an association during treatment phase which decreased again after end of therapy and suggested that an acute effect of matrix metalloproteinase may be the underlying pathomechanism. The article did not differentiate between different FQ and the relevance for inhaled levofloxacin with lower systemic exposure is not established.
Risk factors and risk groups	The elderly population has been identified to be at higher risk to develop aortic aneurysm and aortic dissection. Approximately 75% of aortic dissections are occurring in patients who are ages 40 to 70 years, with the majority between the ages of 50 and 65 years [Levy and Le, 2018]. According to Goldfinger et al. clinical aortic dissection risk factors fall into two broad categories: conditions that contribute to medial degeneration such as Marfan syndrome, Loeys-Dietz syndrome, the vascular form of Ehlers-Danlos syndrome, inflammatory diseases of the aorta, Turner syndrome etc. and those that increase aortic wall stress. The most common condition that increases wall stress is hypertension, present in more than two-thirds of patients with aortic dissection [Goldfinger et al., 2014], which is more likely to harbor in the older population, mainly manifesting through arteriosclerosis. Further identified risk factors compromise of positive family history, pre-existing aortic aneurysms smoking, abrupt and transient increase in blood pressure (e.g., weight lifting, use of cocaine etc.) and prior cardiac surgeries [Levy and Le, 2018,

Important potential risk: Aortic aneurysm/ Aortic dissection	
	Goldfinger et al., 2014]. AAD is three times more common in men than in women, although women tend to present later and experience worse outcomes [Levy and Le, 2018].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 and PL section 2 where advise to immediately consult a physician in an emergency department in case of sudden abdominal, chest or back pain is provided Additional risk minimisation measures: • None

Important potential risk: Heart Valve Regurgitation/ Incompetence	
Evidence for linking the risk to the medicine	Evidence source: Non-clinical and epidemiologic studies, PRAC signal validation. Strength of evidence: In the light of accumulating evidence and biological plausibility suggesting an association of FQ intake with collagen-related disorders, Etminan et al. (2019) undertook a disproportionality analysis combined with an nested case control (NCC) study which showed an about 2-fold increase in risk of another collagen-related disorder - aortic valve regurgitation (AR) and mitral valve regurgitation (MR) associated with use of oral FQs compared with other antibiotics (amoxicillin or azithromycin). A non-clinical study (Guzzardi et al 2019) reported that exposure to ciprofloxacin led to a collagen degradation in aortic myofibroblasts from patients at higher risk for aortic disorders including aortic regurgitation. This finding is consistent with that recorded previously in a mouse model of aortic disease (LeMaire et al 2018) and supports the view that FQ-induced degradation of connective tissue may be implicated in the occurrence of heart valve regurgitation /incompetence. Additionally, several medically confirmed cases of regurgitation / incompetence of heart valves (including all four heart valves: aortic, mitral, tricuspid and pulmonary) have been reported in patients receiving FQs with probable (n=1) or possible (n=13) causal association. Four (4) of these patients received levofloxacin with brand name not specified. However, QUINSAIR can be excluded as it is not approved in the countries where the events occurred. These data suggest that FQs as a class are at least possibly causally associated with the occurrence of heart valve regurgitation/incompetence.
Risk factors and risk groups	The elderly population as well as those patients taking corticosteroids on a regular basis are known to be more at risk for

Important potential risk: Heart Valve Regurgitation/ Incompetence	
	developing heart valve regurgitation/incompetence. Factors that increase the risk for heart valve regurgitation/incompetence also include a congenital heart valve disease, connective tissue disorders e.g. Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis, and infective endocarditis.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and PL section 2 where advise to immediately consult a physician in an emergency department in case of of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities. Additional risk minimisation measures: • None

Important potential risk: Off label use in <18 years (especially musculoskeletal effects)	
Evidence for linking the risk to the medicine	Evidence source: Literature, non-clinical data, clinical trials. Strength of evidence: The prevalence of *P. aeruginosa* infection in CF patients increases with age. However, approximately 20% of patients of less than 5 years will be infected. This rises to 30% in the patients 6-10 years old and 40% in patients 11-17 years old. Quinolones exhibit toxic effects on the immature joint cartilage (epiphyseal-articular complex) in all animal species studied. Although quinolones can also affect the epiphyseal growth plate (in addition to the articular-epiphyseal complex) in new-born or very young animals, severe chondrotoxicity has not been observed after the use of quinolones in children. However, most human data have been derived from nalidixic acid, norfloxacin, and ciprofloxacin, which have either poor tissue penetration or low systemic exposure [Bauchau and Durham, 2004]. During clinical trials for QUINSAIR 85 patients < 18 years of age were included, however no reports on serious adverse musculoskeletal events were reported.
Risk factors and risk groups	The risk of arthropathies in adolescent patients has been reviewed extensively in the literature. However, most reviews are based predominately on clinical data derived from studies with systemic ciprofloxacin and interpretation is difficult owing to the rarity of the event and its non-specificity (i.e. difficulty of specific diagnosis with multiple causal possibilities especially with co-administration of different classes of antibiotics) and the usual short duration of therapy with antibiotics. However, the literature suggests that the risk of arthropathy in adolescents with FQs is low and reversible with management.

Important potential risk: Off label use in <18 years (especially musculoskeletal effects)	
	The musculoskeletal safety of FQs in children was explored by Adefurin and colleagues in a literature review, which included 105 articles reflecting the experience of more than 16,000 ciprofloxacin-treated paediatric patients. Adefurin and colleagues pooled safety data from 23 controlled studies, comprising 6,481 cases and 17,441 controls [Adefurin et al., 2011]. The analysis indicated a 57% increased risk of arthropathy in patients who received FQ (primarily ciprofloxacin) compared to the comparator antibiotics arm [OR 1.57, 95% CI 1.26 to 1.97]. Further analysis of five controlled studies that included only cystic fibrosis patients (227 cases and 391 controls) estimated a 67% increased risk of arthropathy [OR 1.67, 95% CI 1.13 to 2.45]. The authors concluded, "there is an estimated risk of one musculoskeletal AE in every 62.5 [treated] patients, and a 57% increased risk of arthropathy in patients exposed to ciprofloxacin. However, the risk of arthropathy is relatively as low as about 1 in every 62.5 patients and reversible with management" [Adefurin et al., 2011]. The clinical experience with systemic FQs is focused on acute infections [Adefurin et al., 2011]. Chronic use of FQs in the pediatric population has not been reported sufficiently often to draw inferences regarding long-term safety of the class. In adults; however, prolonged administration of systemic levofloxacin has been reported in tuberculosis, Hansen's disease, and chronic osteomyelitis. These reports have showed no alteration of the established safety and tolerability profiles of the drug [Greenberg et al., 2000], [Richeldi et al., 2002, Bundrick et al., 2003, Marra et al., 2005, Senneville et al., 2007, Chauny et al., 2012]. As part of eradication therapy for acute *P. aeruginosa* infections and during treatment of acute exacerbations, pediatric CF patients already experience appreciable systemic exposure to FQs with courses of 500 mg once per day (orally or intravenously) over 10 to 28 days [Schaad et al., 1989, Valerius et al., 1991, Richard et al., 1997, Frederiksen et al., 1997, Smyth and Elborn, 2008, Langton and Smyth, 2014].This previous exposure would be a confounding feature as it can be a potential cause for musculoskeletal complaints in CF pediatric patients . Other systemic antibiotics such as azithromycin can cause similar AEs and complaints. It should also be noted that CF patients might encounter other musculoskeletal AEs as a part of the multisystemic disease itself with resultant nutritional, metabolic and digestive complications. Although levofloxacin is not commonly administered for pediatric age group, its use in pediatric patients is reported to be safe according to available study with long-term follow-up in

Important potential risk: Off label use in <18 years (especially musculoskeletal effects)	
	pediatric patients with respiratory tract infections as well as otitis. [Yee et al., 2002] performed a retrospective and observational study to assess the incidence and relative risk of tendon or joint disorders that occurred following the use of ofloxacin, levofloxacin, and ciprofloxacin. This study involved greater than 6,000 children < 19 years of age with history of fluoroquinolone exposure and a "control group" of children exposed to azithromycin, a macrolide antibiotic which does not have known long-term adverse effects on cartilage, tendons or joints. The calculated risk for tendon or joint disorders was found to be no different in the children treated with FQs when compared to those prescribed azithromycin. In a study by Noel and colleagues, musculoskeletal abnormalities of systemic levofloxacin were studied in 2,523 children, in 3 efficacy studies and a subset of 2,233 of these children who subsequently participated in a long-term 1-year surveillance study [Noel et al., 2007]. Levofloxacin was well tolerated during and for 1 month after therapy, with similar incidences of AEs as reported for the patients randomized to non-fluoroquinolone antibiotics. However, the incidence of at least 1 of the 4 musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) was greater in the levofloxacin-treated children (largely due to reports of arthralgia) at 2 months (2.1% vs 0.9%; p=0.04) and 12 months (3.4% vs 1.8%; p=0.03) than in the non-fluoroquinolone treated children but continued follow-up for 12 months did not show any joint abnormality or structural injuries, respectively. In a published assessment of the musculoskeletal toxicity 5 years after therapy with levofloxacin, Bradley and colleagues reported on the results of a 5-year follow-up safety study of children treated with levofloxacin or comparator in randomized, prospective, comparative studies for acute otitis media and community-acquired pneumonia, which was designed to assess the presence/absence of cartilage injury [Bradley et al., 2014, Bradley et al., 2014]. Of the 2,233 subjects participating in the 12-month follow-up study, 124 of 1,340 (9%) of the levofloxacin subjects, and 83 of 893 (9%) of the comparator subjects were continued for 5-year post treatment assessment. From children identified with a musculoskeletal SAE during years 2 through 5 post treatment, the number that were "possibly related" to drug therapy was equal for both arms: 1 of 1,340 for levofloxacin and 1 of 893 for comparator. Of all cases of musculoskeletal SAE assessed by the Data Safety and Monitoring Committee at 5 years post treatment, no case was assessed as "likely related" to study drug. The authors concluded that with no clinically detectable

Important potential risk: Off label use in <18 years (especially musculoskeletal effects)	
	difference between levofloxacin- and comparator-treated children in musculoskeletal SAEs presenting between 1 and 5 years in these safety studies, risks of cartilage injury with levofloxacin appear to be uncommon, are clinically undetectable during 5 years, or are reversible.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.2, 4.8, 5.1, 5.2 • PL section 1, 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLI-LEVFLAA1-01 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Haemoptysis	
Evidence for linking the risk to the medicine	Evidence source: Literature, clinical trial data. Strength of evidence: Haemoptysis is a complication commonly reported in patients with CF. Major haemoptysis occurs in approximately 1% of children with CF and 6% of the overall CF population [Barben et al., 2003]. A retrospective, observational cohort study of the National CF Patient Registry between the years 1990 to 1999 in the US reported that nearly 1 in 100 patients will have this complication each year [Flume et al., 2005]. Massive haemoptysis occurred with an average annual incidence of 0.87% and in 4.1% of patients overall. The median age for massive haemoptysis was 23 years, and 75% of cases occur in patients >18 years of age [Flume, 2009]. An Israeli cohort of 440 patients reported that 9.1% experienced hemoptysis during the study period. The mean age at the first episode of haemoptysis was 18.4±7. 4 years. 25% of haemoptysis cases occurred before age 13 [Efrati et al., 2008]. The fact that the incidence of haemoptysis in clinical trials was similar in the MP-376 group compared to the placebo group and tobramycin group may be explained by both the known background incidence of haemoptysis in these patients and an association with inhaled therapies in general.
Risk factors and risk groups	Massive haemoptysis is occurring more commonly in older patients with more advanced lung disease. Flume and colleagues reported that the occurrence of massive haemoptysis was more prevalent in adult patients. Only 25% of patients with this complication had massive haemoptysis prior to the age of 18 years, and half of the patients with this complication had their first episode between the ages of 18 years and 30 years [Flume et

	al., 2005]. Patients with *Staphylococcus aureus* [OR, 1.3] and diabetes [OR, 1.1] had increased risk of massive haemoptysis. There was no increased occurrence by sex, but it was more prevalent in older patients (mean age, 24.2±8.7 years [±SD]) with more severe pulmonary impairment. Similarly, Efrati et al reported that pulmonary exacerbation was the precipitating factor of haemoptysis in 90% of the cases [Efrati et al., 2008].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4, 4.8 • PL section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLI-LEVFLAA1-01 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Evidence source: Literature, non-clinical data, clinical trial data. Strength of evidence: Changes in the liver function tests were observed in non-clinical-trials with MP-376. In general, hepatotoxicity is a known class effect for FQs, ranging from increased transaminases to cholestatic hepatitis and fulminant hepatitis and has been reported with varying frequency with other FQs including oral levofloxacin, ciprofloxacin and moxifloxacin. Whilst clinical trial experience has not revealed any strong evidence of a causal relationship between hepatotoxicity and MP-376, cases of hepatic necrosis up to fetal hepatic failure have been reported with systemically administered levofloxacin, primarily in patients with severe underlying diseases (e.g. sepsis). Furthermore, liver diseases are a known risk factor for the patient's underlying disease, one third of the patients with CF during long-term follow-up are affected including elevated transaminases, hepatosteatosis, and biliary tract disease. About 20 to 60% have hepatic steatosis, 20 to 30% have focal biliary cirrhosis with 15% having multilobular biliary cirrhosis, and 15% have gall stones. Liver disease was the primary cause of death in 2.5%, making it the second most common cause of death in CF patients [Herrmann et al., 2010].
Risk factors and risk groups	In CF patients, there is evidence of an association between age and hepatobiliary disease. Approximately 5-10% of the CF patients develop multilobular cirrhosis during the first decade of life. The incidence of liver disease in CF patients during this decade of life is 1.8 to 2.5/ 100 patient-years and significantly decreases during the second decade [Debray, 2012]. Globally 30-

Important potential risk: Hepatotoxicity	
	40% of children develop liver damage before age 12. This statement was confirmed by three studies, the aim of the first study [Lindblad et al., 1999] was to evaluate the natural history of CF-associated liver disease over a 15-year period in a well-controlled population of patients with CF. 124 patients were followed up by yearly LFTs. Fifteen patients were followed up with liver biopsies throughout the whole study period. More than 50% of the patients had pathological LFTs in infancy, later being normalized. Approximately 25% of children 4 years of age or older had biochemical markers of liver disease during the study period. In about 10% of the patients, cirrhosis or advanced fibrosis was confirmed at biopsy and 4% of patients had cirrhosis with clinical liver disease. Severe liver disease developed mainly during pre-puberty and puberty. Of the 15 patients prospectively followed up with liver biopsies, only 3 had progressive fibrosis. In the second study performed by Colombo C. et al. assessed prospectively the incidence and risk factors of this complication, and its impact on the clinical course of CF. Between 1980 and 1990, the authors enrolled 177 CF patients without liver disease in a systematic clinical, laboratory, ultrasonography screening program of at least a 10-year duration. The results showed that during a 14-year median follow-up (2,432 patient-years), 48 patients developed liver disease, with cirrhosis already present in 5 of them and the incidence rate was 1.8% (95% confidence interval: 1.3-2.4), with sharp decline after the age of 10 years [Colombo et al., 2002]. The aim of the third study by Lamireau et al. was to describe the prevalence of liver disease in a cohort of 241 CF patients [Lamireau et al., 2004]. The results showed that the prevalence of liver disease was 18, 29, and 41% after 2, 5 and 12 years, respectively, and did not increase thereafter [Lamireau et al., 2004].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 and PL section 4 where advice to stop treatment and contact the doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen is provided • SmPC section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLI-LEVFLAA1-01 See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Decreased susceptibility to *P. aeruginosa*	
Evidence for linking the risk to the medicine	Evidence source: Literature, clinical trial data. Strength of evidence: Treatment of signs and symptoms of pulmonary infection with antibiotics without complete clearance of organisms from the airway leads to gradual selection for bacterial strains that are less susceptible to antibiotics. According to the National Nosocomial Infections Surveillance (NNIS) System [NNIS, 2004], *P. aeruginosa* is among the leading pathogens causing nosocomial infections and is the most common cause of pneumonia in the medical intensive care unit. With the widespread use of FQs, an alarming increase in the prevalence of FQ resistance among *P. aeruginosa* strains has been seen [Hsu et al., 2005]. During the clinical trial program, only very modest decreases in levofloxacin susceptibilities of *P. aeruginosa* isolates were associated with multiple cycles of MP-376 treatment, and similar changes were observed among patients not receiving MP-376. Taken together, these data indicated that cyclic treatment with QUINSAIR does not substantially increase risk for selection for *P. aeruginosa* isolates with decreased antibiotic susceptibility among CF patients with chronic *P. aeruginosa* infection, for whom standard of care is long term administration of antipseudomonal antibiotics.
Risk factors and risk groups	*P. aeruginosa* is one of the most common and important opportunist gram-negative pathogens causing hospital-acquired infections [Yang et al., 2015]. In a study performed by [Hsu et al., 2005] risk factors that were found to be significantly associated with the acquisition of FQ resistant *P. aeruginosa* were nosocomial residence, diabetes as a co-morbid condition, and exposure to a FQ within 30 days before isolation of the organism. Furthermore, *P. aeruginosa* infection or colonization within the previous year, mechanical ventilation, malignant disease and history of COPD have been identified as independent risk factors for multidrug-resistant *P. aeruginosa* infection [Hirsch and Tam, 2010].
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4, 5.1 • PL section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLI-LEVFLAA1-01 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety	
Risk minimisation measures	No risk minimisation measures

II C. Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

CLI-LEVFLAA1-01

Purpose of the study: CF is an inherited, long-term debilitating and life-threatening disease affecting approximately 0.8 people in 10,000 in the EU. The accumulation of thick mucus in the lungs in CF patients allows bacteria to grow and colonize more easily, causing chronic infections. *P. aeruginosa* is a frequent cause of chronic pulmonary infections in CF patients. The standard of care for treating CF patients with *P. aeruginosa* has been to use inhaled antibiotic therapies chronically in order to improve lung function and quality of life and reduce the occurrence of pulmonary exacerbations. QUINSAIR is a formulation of levofloxacin (levofloxacin hemihydrate) for aerosol administration intended for the management of chronic pulmonary infections due to *P. aeruginosa* in adult CF patients and was well-tolerated in clinical studies when administered at 240 mg BID (twice daily) for up to six consecutive cycles (N=56 who received up to 6 cycles), each comprising 28 days on treatment and 28 days off treatment. QUINSAIR is intended for use as long as the physician considers the patient is receiving clinical benefit. Secondary data from the UK CF Registry and in Germany CF Registry, will be used in this observational post-authorization safety study (PASS) to evaluate the long-term safety of QUINSAIR over a 5-year period. The incidence and occurrence over time of each adverse events of special interest (AESIs) concerning hepatotoxicity, haemoptysis and tendon rupture, and the safety of off-label use, specifically musculoskeletal events in patients <18 years of age, are to be evaluated in this study. In addition, data on discontinuations of treatment due to adverse events (AEs) in all patients and development of antimicrobial resistance of *P. aeruginosa* isolated from QUINSAIR-treated patients will be collected. Comparison data will be obtained from patients who are treated with other approved inhaled antibiotics e.g. inhaled formulations of tobramycin, aztreonam lysine, colistimethate and levofloxacin and not receiving QUINSAIR.

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

There are no studies required for QUINSAIR.