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# Summary of the risk management plan (RMP) for Quinsair (levofloxacin)

This is a summary of the risk management plan (RMP) for Quinsair, which details the measures to be taken in order to ensure that Quinsair is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Quinsair, which can be found on Quinsair's EPAR page.

## Overview of disease epidemiology

Quinsair is an antibiotic used for treating long-term lung infection caused by the bacteria *Pseudomonas aeruginosa* in adults who have cystic fibrosis. Cystic fibrosis is an inherited, long-term debilitating and life-threatening disease in which there is an accumulation of thick mucus in the lungs that allows bacteria to grow more easily, causing infections. *P. aeruginosa* is a frequent cause of infections in cystic fibrosis patients.

Cystic fibrosis affects approximately 0.8 people in 10,000 in the European Union. Approximately 20% of patients with cystic fibrosis aged up to 5 years are infected with *P. aeruginosa*; the prevalence of *P. aeruginosa* infections increases with age, and by the age of 25 to 34 years approximately 80% of patients with cystic fibrosis are infected with *P. aeruginosa*.

## Summary of treatment benefits

Quinsair is available as a nebuliser solution. It contains the active substance levofloxacin, which belongs to the group of antibiotics known as 'fluoroquinolones'.

Quinsair has been investigated in two main studies in patients who had cystic fibrosis with *P. aeruginosa* lung infection. The first study, which involved 330 patients, compared Quinsair with placebo (a dummy treatment), while the second, involving 282 patients, compared it with another inhaled antibiotic (tobramycin). In both studies, the majority of patients were adults.

In the first study, Quinsair was shown to be better than placebo at improving the patients' forced expiratory volume in one second ($FEV_1$), adjusted for the patient's age, height and sex. $FEV_1$ is the most air a person can breathe out in one second. Following 28 days of treatment, the patients taking Quinsair had an improvement in $FEV_1$ of 1.73%, while for patients taking placebo the improvement in $FEV_1$ was of around 0.43%. However, the study failed to show that Quinsair is more effective than placebo at increasing the time it took before the patients had an exacerbation (flare-up) of their disease.

The second study showed that Quinsair was at least as good as tobramycin at improving $FEV_1$ following 1 to 3 treatment cycles.

## Unknowns relating to treatment benefits

It is not known whether patients aged 65 years and above, and patients with moderate or severe kidney impairment benefit from treatment with Quinsair, as these patients were not included in clinical trials. In addition, there is no information on the effects of Quinsair when used long term.

## Summary of safety concerns

***Important identified risks***

| Risk | What is known | Preventability |
|---|---|---|
| Narrowing of the airways (Bronchospasm) | As with all inhaled medicines, there is the possibility that the airways in the lungs may react to cause their narrowing. | The risk of narrowing of the airways can be reduced by taking a specific medicine by inhalation known as short-acting bronchodilator or reliever, prior to taking Quinsair. |
| Inflammation of the tendons (Tendinitis) | When levofloxacin (the active substance in Quinsair) is taken by mouth or by injection, it can cause inflammation of the tendons, which can cause pain and reduce mobility if not treated. As Quinsair is an inhaled treatment, the amount of levofloxacin in the blood is lower than with levofloxacin given by mouth or injection, and hence the risk is thought to be lower. In clinical trials, tendinitis was reported as an uncommon side effects (occurring in up to 1 patient in 100). | The risk of tendinitis is greater in patients aged over 60 years, in patients taking Quinsair in doses greater than 1,000 mg and in patients who are taking steroids at the same time as Quinsair. Patients should consult their doctor if they develop any musculoskeletal (muscle and bone) pain. If tendinitis does develop, treatment with Quinsair should be stopped and medical treatment with immobilisation for the affected tendon should be started. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Bacterial growth in the nebuliser handset | The nebuliser can become moist with use and this provides a good environment for bacteria to grow. The nebuliser handset must be cleaned immediately after use and disinfected at least once a day in order to prevent bacteria from growing. If the handset is not cleaned, there is a risk of bacterial growth. |
| Tendon rupture | In patients treated with levofloxacin by mouth or by injection, there have been reports of tendinitis which could lead to rupture of a tendon. Rupture of a tendon is a serious condition which often requires surgical treatment or prolonged immobilisation. No cases of tendon rupture were seen in clinical trials with Quinsair. |
| Muscle and joint effects in children (under 18 years of age) | Studies of Quinsair in animals have demonstrated abnormal effects on the cartilage of some joints in young animals. It is not known if this also occurs in children.<br>In clinical trials there were a few reports of joint pain in children of 14 and 16 |

| Risk | What is known |
|---|---|
| | years of age. |
| Coughing up blood (Haemoptysis) | Cough and coughing up blood can occur in patients following the use of inhaled medicines. In clinical trials, there were some reports of this side effect, but these occurred at a similar rate in patients treated with Quinsair to those treated with tobramycin.<br>Quinsair should only be given to patients with significant haemoptysis if the benefits are considered to outweigh the risk of inducing further bleeding. |
| Liver damage (Hepatotoxicity) | Quinsair is a fluoroquinolone and other fluoroquinolones have been associated with liver damage when taken by mouth. Hence this is considered a potential risk with Quinsair.<br>In clinical trials, there was a similar rate of reports of abnormalities in liver function between patients treated with Quinsair and those treated with tobramycin. Patients with cystic fibrosis often have abnormalities of liver function due to their disease. |
| Effects on the blood (Haematological effects) | Other fluoroquinolones have been associated with blood abnormalities when taken by mouth. Hence this is considered to be a potential risk with Quinsair.<br>In clinical trials, there were a few reports of minor blood abnormalities and the rate was similar between patients treated with Quinsair and those treated with tobramycin. |
| Severe skin reactions (Severe cutaneous adverse reactions) | In clinical trials there were no reports of severe skin reactions. However, other fluoroquinolones have been associated with severe skin reactions when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Severe allergic reactions (Severe hypersensitivity reactions) | Quinsair is an antibiotic and severe hypersensitivity reactions can occur with antibiotics. However, in clinical trials there were no reports of severe allergic reactions. Hence this is considered to be a potential risk with Quinsair. |
| Infection occurring after or on top of an earlier infection (Superinfection) | Sporadic cases of secondary infections in cystic fibrosis patients already chronically infected with certain bacteria have been reported. Hence this is considered to be a potential risk with Quinsair. |
| Severe diarrhoea due to changes to the normal bacteria in the gut (*C. difficile*-associated disease) | Antibiotics can kill bacteria and as a result they can also kill some of the normal bacteria in the gut. This may then allow for harmful bacteria to colonise the gut and produce a severe form of diarrhoea, which is known to occur with many antibiotics. In clinical trials there were no reports of this effect occurring with Quinsair. However, as it can occur with antibiotics in general, it is considered to be a potential risk with Quinsair. |
| Increased bacteria resistance (Decreased susceptibility to *P. aeruginosa*) | In general, prolonged use of antibiotics can result in changes of the bacteria that allow them to survive the antibiotic treatment and become resistant to it. Thus this is considered to be a potential risk with Quinsair. |
| Unapproved use (off-label use) in patients with chronic obstructive pulmonary (COPD) | Patients with COPD may get lung infections with *P. aeruginosa*. However, the safety and benefits of Quinsair in these patients is not known and Quinsair is not approved for use in this condition. |

| Risk | What is known |
|---|---|
| disease | |
| Discontinuation of treatment due to impaired/unpleasant taste | Quinsair can cause an impaired or unpleasant taste in the mouth and there is a potential risk that patients may therefore discontinue treatment with Quinsair. |
| Heart rhythm disorder that can potentially cause fast or abnormal heartbeats (QT Prolongation/ Torsades de Pointes) | Other fluoroquinolones have been associated with life-threatening changes in the heart rhythm when taken by mouth. Hence this is considered to be a potential risk with Quinsair. Patients with pre-existing heart disease, elderly people, and those taking other medicines that can also cause this effect are most at risk. |
| Retinal detachment | Cases of retinal detachment have been reported with antibiotics similar to levofloxacin when they are taken by mouth. Hence this is considered to be a potential risk with Quinsair. If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately. |
| Epileptic fits in patients who are predisposed to epileptic fits (Seizures in patients predisposed to seizures) | Antibiotics similar to levofloxacin have been associated with epileptic fits in predisposed patients when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Damage to the nerves in arms and legs (Peripheral neuropathy) | Other fluoroquinolones have been associated with damage to the nerves in the arms and legs when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Worsening of a muscle disease known as myasthenia gravis (Exacerbation of myasthenia gravis) | Other fluoroquinolones have been associated with the worsening of a muscle disease known as myasthenia gravis when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Psychiatric problems (Psychotic disorders) | Antibiotics similar to levofloxacin have been associated with psychiatric problems when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Changes in blood sugar levels (Dysglycaemia/ hypoglycaemia) | Antibiotics similar to levofloxacin have been associated with changes in blood sugar levels when taken by mouth. Hence this is considered to be a potential risk with Quinsair. |
| Use in pregnancy and breastfeeding | There is insufficient data on the safety of Quinsair on the developing embryo. Animal studies suggest that fluoroquinolones may damage the cartilage of the growing organism. Hence, the use of Quinsair during pregnancy and breastfeeding is contraindicated. |

***Missing information***

| Risk | What is known |
|---|---|
| Use in patients 65 years or older | In clinical trials, patients of 65 years of age and above were not sufficiently studied. Therefore it is not known whether Quinsair is as effective or as safe in this patient population. |
| Long-term safety | In clinical trials, the maximum duration of treatment was six 28-day cycles of treatment. Therefore the effect of Quinsair when used for longer periods is not known. |
| Use in patients with moderate to severe kidney failure | In clinical trials, patients with moderate to severe kidney failure were not sufficiently studied. Therefore it is not known whether Quinsair is as effective or as safe in this patient population. |

## Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Quinsair can be found on Quinsair's EPAR page.

This medicine has no additional risk minimisation measures.

## Planned post-authorisation development plan

***List of studies in post-authorisation development plan***

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Post authorisation safety study with CF registries in European countries where feasible | To monitor long-term safety.<br><br>To monitor adverse events leading to discontinuation and development of multidrug-resistant *P. aeruginosa*. | • Off label use in patients below 18 years;<br>• Discontinuation due to side effects;<br>• Decreased *P. aeruginosa* susceptibility to levofloxacin;<br>• Long-term safety;<br>• Liver toxicity;<br>• Haemoptysis (coughing up blood);<br>• Tendon rupture. | Planned | Cumulative analyses will be performed at 1 year intervals for 5 years, with the final study report expected in 2022 |
| MPEX 211: Open label randomised | To compare the safety and efficacy of | Safety and efficacy in patients less than 12 | Planned | July 2019 (final report) |

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| phase 3b trial to evaluate the efficacy and safety of MP-376 inhalation solution versus tobramycin inhalation solution in stable cystic fibrosis patients aged 5-11 years | Quinsair and tobramycin inhalation solution administered over multiple cycles in children ages 5 to 11.<br><br>To explore the musculoskeletal safety of Quinsair and tobramycin inhalation solution when administered over multiple cycles in children ages 5 to 11. | years. | | |
| MPEX 212 Open-label phase 3b trial to evaluate activity and safety of MP-376 in paediatric patients aged 28 days to 17 years with cystic fibrosis (CF) and new-onset of respiratory tract-cultured *Pseudomonas aeruginosa* | Patients will receive 28 days of Quinsair and will be followed for 28 weeks to determine the duration of antimicrobial efficacy and to explore the long-term safety of Quinsair. | Safety in paediatric population including patients from 28 days to 17 years of age. | Planned | August 2019 |

***Studies which are a condition of the marketing authorisation***

The post authorisation safety study with cystic fibrosis registries in European countries is a condition of the marketing authorisation.

## Summary of changes to the risk management plan over time

***Major changes to the Risk Management Plan over time***

Not applicable.

This summary was last updated in 02-2015.