ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Quinsair 240 mg nebuliser solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of nebuliser solution contains levofloxacin hemihydrate equivalent to 100 mg of levofloxacin. Each ampoule contains 240 mg of levofloxacin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser solution.

Clear, pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quinsair is indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis (CF, see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial medicinal products.

4.2 Posology and method of administration

Posology

The recommended dosage is 240 mg (one ampoule) administered by inhalation twice daily (see section 5.2). The doses should be inhaled as close as possible to 12 hours apart.

Quinsair is taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. Cyclical therapy may be continued for as long as the physician considers that the patient is obtaining clinical benefit.

If a dose is missed, it should be taken as soon as the patient remembers providing that at least an 8-hour interval is allowed before inhaling the next dose. Patients should not inhale the contents of more than one ampoule to compensate for the missed dose.

If acute symptomatic bronchospasm occurs after receiving Quinsair, patients may benefit from the use of a short-acting inhaled bronchodilator at least 15 minutes to 4 hours prior to subsequent doses (see sections 4.4 and 4.8).

Elderly patients (≥ 65 years old)
The safety and efficacy of Quinsair in elderly patients with CF have not been established.

Renal impairment
Doses do not need to be adjusted in patients with mild to moderate renal impairment . Quinsair is not recommended for use in patients with severe renal impairment.

Hepatic impairment
No dose adjustment is required (see section 5.2).

Paediatric population
The safety and efficacy of Quinsair in children aged < 18 years old have not yet been established. Currently available data are described in sections 4.8, 5.1, 5.2 and 5.3 but no recommendation on a posology can be made.

Method of administration

Inhalation use.

Once an ampoule is opened, the contents should be used immediately (see section 6.6).

For patients taking multiple inhaled therapies, the recommended order of administration is as follows:
1. Bronchodilators;
2. Dornase alfa;
3. Airway clearance techniques;
4. Quinsair;
5. Inhaled steroids.

Quinsair should only be used with the Zirela Nebuliser Handset (including a Zirela Aerosol Head) provided in the pack connected to an eBase Controller or an eFlow rapid Control Unit (see section 6.6). The Manufacturer's Instructions for Use of the Zirela Nebuliser System should be reviewed prior to the first use of Quinsair.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinolones or to any of the excipients listed in section 6.1;
- History of tendon disorders related to fluoroquinolone administration;
- Epilepsy;
- Pregnancy;
- Breast-feeding.

4.4 Special warnings and precautions for use

The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. including angioedema and anaphylactic shock).

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with systemic administration of levofloxacin (see section 4.8).

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with systemically administered levofloxacin, primarily in patients with severe underlying diseases (e.g. sepsis, see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval (see sections 4.5, 4.8 and 4.9) such as, for example:

- Congenital long QT syndrome.
- Concomitant use of active substances that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia).
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Elderly patients and women may be more sensitive to QTc-prolonging medicinal products. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures (see section 4.8). Levofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or on concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline (see section 4.5).

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases, these have progressed to suicidal thoughts and self-endangering behaviour - sometimes after only a single dose of levofloxacin (see section 4.8). Caution is recommended if levofloxacin is used in psychotic patients or in patients with a history of psychiatric disease.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with levofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing serious adverse reactions, including deaths and the requirements for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially, but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, patients receiving daily doses of 1,000 mg levofloxacin, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Tendinitis was reported in patients with CF receiving Quinsair as an uncommon adverse reaction during clinical trials (see section 4.8).

Bronchospasm

Bronchospasm is a complication associated with inhaled therapies including Quinsair (see section 4.8). If acute, symptomatic bronchospasm occurs after receiving treatment, patients may benefit from the use of a short-acting inhaled bronchodilator prior to subsequent doses (see section 4.2).

Haemoptysis

The use of inhaled medicinal products may induce a cough reflex. Administration of Quinsair in patients with clinically significant haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone medicinal products. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients treated with vitamin K antagonists

Due to possible increases in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these active substances are given concomitantly (see section 4.5).

Dysglycaemia

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicinal product (e.g. glibenclamide) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to life-threatening, the most severe form of which is pseudomembranous colitis.

Resistance to levofloxacin, other antibacterial medicinal products and treatment-emergent microorganisms

The development of fluoroquinolone-resistant *P. aeruginosa* and superinfection with fluoroquinolone-insusceptible microorganisms represent potential risks associated with the use of Quinsair. If superinfection occurs during therapy, appropriate measures should be taken.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium) during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific methods.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rapture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
- for 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
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rapture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin

Levofloxacin is primarily excreted unchanged in the urine and metabolism is minimal (see section 5.2). Interactions with CYP inhibitors or inducers are thus not expected.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other substances which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine
The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both active substances are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance. Caution should be exercised when levofloxacin is coadministered with active substances that affect the tubular renal secretion such as probenecid and cimetidine, especially in patients with renal impairment.

Other relevant information
Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following active substances: calcium carbonate, digoxin, glibenclamide and ranitidine.

Effect of levofloxacin on other medicinal products

CYP1A2 substrates
In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2) indicating that levofloxacin is not a CYP1A2 inhibitor.

CYP2C9 substrates
An *in vitro* study indicated a low potential for interaction between levofloxacin and CYP2C9 substrates.

Interactions mediated by effects on transporters
In vitro studies demonstrated that inhibition of the key transporters associated with drug disposition in the kidney (organic anion-transporting polypeptide-1B1 (OATP1B1), OATP1B3, organic anion transporter-1 (OAT1), OAT3 and organic cationic transporter-2 (OCT2)) at exposures following inhalation of 240 mg levofloxacin twice daily is low.

Furthermore, clinical data do not suggest interaction with P-glycoprotein (P-gp) substrates such as digoxin.

Ciclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4).

Active substances known to prolong the QT interval
Levofloxacin should be used with caution in patients receiving active substances known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of levofloxacin in pregnant women. Animal studies with levofloxacin do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

However, in the absence of human data and findings in non-clinical studies suggesting a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, use of Quinsair is contraindicated during pregnancy (see sections 4.3 and 5.3).

Breast-feeding

There is insufficient information on the excretion of levofloxacin/metabolites in human milk; however, other fluoroquinolones are excreted in breast milk.

In the absence of human data and findings in non-clinical studies suggesting a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, use of Quinsair is contraindicated in breast-feeding women (see sections 4.3 and 5.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Quinsair has minor influence on the ability to drive and use machines. Some adverse reactions (e.g. fatigue, asthenia, visual disturbances, dizziness) may impair patient's ability to concentrate and react. Patients who experience such symptoms should be advised not to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were cough/productive cough (54%), dysgeusia (30%) and fatigue/asthenia (25%).

Tabulated list of adverse reactions reported with Quinsair

The adverse reactions with at least a reasonable possibility of a causal relationship with Quinsair are presented according to the MedDRA System Organ Classification. The adverse drug reactions are ranked by frequency with the most frequent reactions first. The frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon
Infections and infestations		Vulvovaginal mycotic infection	Oral fungal infection
Blood and lymphatic system disorders			Anaemia*, Neutropenia*
Immune system disorders			Hypersensitivity*
Metabolism and nutrition disorders	Anorexia*		
Psychiatric disorders[1]		Insomnia*	Anxiety*, Depression*
Nervous system disorders[1]	Dysgeusia	Headache, Dizziness*	Hyposmia*, Somnolence*, Peripheral neuropathy
Eye disorders[1]			Visual disturbance*
Ear and labyrinth disorders[1]		Tinnitus*	Hearing loss*
Cardiac disorders**			Tachycardia*
Respiratory, thoracic and mediastinal disorders	Cough/productive cough, Dyspnoea, Changes in bronchial secretions (volume and viscosity)*, Haemoptysis*	Dysphonia	Bronchospasm***, Bronchial hyper-reactivity, Obstructive airways disorder
Gastrointestinal disorders		Nausea, Vomiting, Abdominal pain*, Diarrhoea*, Constipation*	Retching, Dyspepsia*, Flatulence*
Hepatobiliary disorders			Hepatitis*, Hyperbilirubinaemia*
Skin and subcutaneous tissue disorders		Rash	Urticaria*, Pruritus*
Musculoskeletal and connective tissue disorders[1]		Arthralgia, Myalgia*	Tendinitis, Costochondritis, Joint stiffness
Renal and urinary disorders			Renal failure*
General disorders and administration site conditions[1]	Fatigue/asthenia, Exercise tolerance decreased	Pyrexia	

System organ class	Very common	Common	Uncommon
Investigations	Forced expiratory volume decreased*	Alanine aminotransferase increased, Aspartate aminotransferase increased, Pulmonary function test decreased*, Blood glucose increased and decreased*, Blood creatinine increased*, Breath sounds abnormal*	Liver function test abnormal, Blood alkaline phosphatase increased*, Electrocardiogram QT prolonged*, Eosinophil count increased*, Platelet count decreased*

[1] Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).
* Adverse events with uncertain relatedness to Quinsair but which are known to be associated with systemic administration of levofloxacin and/or are plausibly associated with Quinsair and were reported more frequently than with placebo in clinical studies.
** Cases of aortic aneurysm and dissection, sometimes complicated by rapture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).
*** See paragraph below for further details.

Tabulated list of additional adverse reactions reported following systemic administration of levofloxacin

The adverse reactions with at least a reasonable possibility of a causal relationship with levofloxacin are presented according to the MedDRA System Organ Classification. The adverse drug reactions are ranked by frequency with the most serious reactions first. The frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

System organ class	Uncommon	Rare	Not known
Blood and lymphatic system disorders			Pancytopenia*, Agranulocytosis*, Haemolytic anaemia*
Immune system disorders		Angioedema	Anaphylactic shock, Anaphylactoid shock
Endocrine disorders		Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	
Metabolism and nutrition disorders		Hypoglycaemia	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders[1]	Confusional state, Nervousness	Psychotic reactions (e.g. hallucination, paranoia), Agitation, Abnormal dreams, Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt

System organ class	Uncommon	Rare	Not known
Nervous system disorders[1]	Tremor	Convulsion, Paraesthesia	Peripheral sensory neuropathy, Peripheral sensory motor neuropathy, Dyskinesia, Extrapyramidal disorder, Syncope, Benign intracranial hypertension
Eye disorders[1]			Transient vision loss
Ear and labyrinth disorders[1]	Vertigo		
Cardiac disorders**		Palpitation	Ventricular tachycardia, Ventricular arrhythmia and torsade de pointes
Vascular disorders**		Hypotension	
Respiratory, thoracic and mediastinal disorders			Pneumonitis allergic
Hepatobiliary disorders			Jaundice and severe liver injury, including cases with fatal acute liver failure
Skin and subcutaneous tissue disorders	Hyperhidrosis	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction, Leukocytoclastic vasculitis, Stomatitis
Musculoskeletal and connective tissue disorders[1]		Muscular weakness	Rhabdomyolysis, Tendon rupture, Ligament rupture, Muscle rupture, Arthritis
General disorders and administration site conditions[1]			Pain (including pain in back, chest and extremities)

* See paragraph below for further details.

[1] Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rapture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4)

Description of selected adverse reactions

If acute, symptomatic bronchoconstriction occurs after receiving Quinsair, patients may benefit from the use of a short-acting inhaled bronchodilator prior to subsequent doses (see sections 4.2 and 4.4).

Serious haematological adverse reactions such as pancytopenia, agranulocytosis and haemolytic anaemia have been reported following systemic administration of levofloxacin. Their frequency cannot be estimated from available data.

Paediatric population

In clinical trials, 51 adolescents with CF (≥ 12 to < 18 years old) received Quinsair 240 mg twice daily and 6 adolescents with CF received Quinsair 120 mg (n = 3) or 240 mg (n = 3) once daily. In addition, 14 children with CF (≥ 6 to < 12 years old) and 13 adolescents with CF (≥ 12 to < 17 years old) received Quinsair 180 mg or 240 mg once daily for 14 days. Based on these limited data, there does not appear to be any clinically relevant difference in the safety profile of Quinsair in these subsets of the paediatric population compared to adults. However, two cases of arthralgia have been observed in children in clinical studies with Quinsair and long-term safety data are missing especially considering the effects on cartilage observed in animals (see sections 4.2 and 5.3).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, symptomatic treatment should be implemented. The patient should be observed and appropriate hydration maintained. ECG monitoring should be undertaken because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD), are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, fluoroquinolones ATC code: J01MA12

Mechanism of action

The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial DNA gyrase and topoisomerase IV enzymes.

PK/PD relationship

The parameters associated with the antibacterial effects of levofloxacin are the C_{max}/MIC and AUC/MIC ratios (C_{max} = maximum concentration at the site of infection, AUC = area under the curve and MIC = minimal inhibitory concentration).

Resistance

Resistance to levofloxacin is most often acquired through a stepwise process by target site mutations in DNA gyrase and topoisomerase IV. Reduced susceptibility to levofloxacin can also result from

acquisition of plasmids encoding proteins that protect these targets from inhibition. Reduced bacterial permeability (common in *P. aeruginosa*) and efflux mechanisms may also confer or contribute to resistance.

Cross-resistance between levofloxacin and other fluoroquinolones is observed.

Breakpoints

Established susceptibility breakpoints for systemic (oral or intravenous) administration of levofloxacin are not applicable to delivery by inhalation.

Clinical efficacy

Clinical efficacy was demonstrated in two placebo-controlled studies and one active-comparator study in 448 patients randomised to receive Quinsair 240 mg twice daily.

Two randomised, double-blind, single-cycle, placebo-controlled clinical trials (Studies 204 and 207) in patients with CF chronically infected with *P. aeruginosa* were conducted. Adult and adolescent (≥ 12 to < 18 years old and weighing ≥ 30 kg) patients who had a FEV_1 percent predicted between 25% and 85% were enrolled. All patients had also received a minimum of 3 courses of inhaled anti-pseudomonal antimicrobial therapy in the 12 months (Study 204) or 18 months (Study 207) prior to entry into the study, but none in the 28 days immediately preceding study entry. In addition to study drug, patients remained on standard of care treatment for chronic pulmonary infection. A total of 259 patients were randomised to Quinsair 240 mg twice daily for 28 days (≥ 18 years, n = 226; ≥ 12 to < 18 years old, n = 33) and 147 were randomised to placebo (≥ 18 years, n = 127; ≥ 12 to < 18 years old, n = 20). These two placebo-controlled studies showed that 28 days of treatment with Quinsair 240 mg twice daily resulted in significant improvement in relative change from baseline in FEV_1 percent predicted compared to placebo (see Table 1).

Table 1: FEV_1 Percent predicted relative change from baseline to Day 28 in placebo-controlled efficacy and safety studies of Quinsair in patients with CF

FEV_1 percent predicted	**Supportive studies**			
	Study 207 (ITT)		**Study 204 (ITT) [a]**	
	Placebo	**Quinsair 240 mg BID**	**Placebo**	**Quinsair 240 mg BID**
	N = 110	N = 220	N = 37	N = 39
≥ 12 to < 18 years, n (%)	16 (14.5)	30 (13.6)	4 (10.8)	3 (7.7)
≥ 18 years, n (%)	94 (85.5)	190 (86.4)	33 (89.2)	36 (92.3)
Baseline mean (SD)	56.32 (15.906)	56.53 (15.748)	52.4 (13.42)	48.8 (15.15)
Relative change from Baseline to Day 28 LS Mean (SE)	1.24 (1.041)	3.66 (0.866)	-3.46 (2.828)	6.11 (2.929)
Treatment Difference at Day 28 [95% CI] [b]	2.42 [0.53, 4.31]; P = 0.012 [c]		9.57 [3.39, 15.75]; P = 0.0026 [c]	

CI = Confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat (all patients randomised); P = P value; SD = standard deviation; SE = standard error; ANCOVA = analysis of covariance.
[a] ANCOVA with terms for treatment, region, age (16 to 18 years, > 18 years), and baseline FEV_1 percent predicted as quartiles. (Note: In Study 204, an additional 38 patients were randomised to Quinsair 120 mg once daily (≥ 18 years, n = 35; ≥ 16 to < 18 years old, n = 3) and an additional 37patients were randomised to Quinsair 240 mg once daily (≥ 18 years, n = 34; ≥ 16 to < 18 years old, n = 3).)
[b] LS Mean difference for Quinsair minus placebo.
[c] Tested using alpha of 0.05.

Study 209 (Core Phase) was a randomised, open-label, parallel group, active-controlled, non-inferiority study comparing Quinsair to tobramycin inhalation solution (TIS) over 3 treatment cycles. Each treatment cycle included 28 days of treatment with Quinsair 240 mg twice daily or TIS 300 mg twice daily followed by 28 days without inhaled antibiotics. Adult and adolescent

(≥ 12 to < 18 years old and weighing ≥ 30 kg) patients who had a FEV_1 percent predicted between 25% and 85% were enrolled. All patients had also received at least 3 courses of TIS in the 12 months prior to entry into the study, but none in the 28 days immediately preceding study entry. In addition to study drug, patients remained on standard of care treatment for chronic pulmonary infection. A total of 189 patients were randomised to Quinsair 240 mg twice daily (≥ 18 years, n = 170; ≥ 12 to < 18 years old, n = 19) and 93 were randomised to TIS (≥ 18 years, n = 84; ≥ 12 to < 18 years old, n = 9). Results obtained for the primary and key secondary endpoints are provided in Table 2.

Table 2: Results for the primary and key secondary endpoints in the active-controlled efficacy and safety study of Quinsair in patients with CF

Parameter	**Pivotal Study – Study 209 (Core Phase; ITT)**		
	TIS 300 mg BID N = 93	**Quinsair 240 mg BID N = 189**	**Treatment Difference [a]**
≥ 12 to < 18 years, n (%)	9 (9.7)	19 (10.1)*	
≥ 18 years, n (%)	84 (90.3)	170 (89.9)	
FEV_1 Percent predicted Baseline mean (SD)	53.20 (15.700)	54.78 (17.022)	
Primary endpoint:			
FEV_1 Relative change from Baseline to Day 28 of Cycle 1	N = 93 0.38 (1.262) [b]	N = 189 2.24 (1.019) [b]	LS mean [95% CI]: 1.86 [-0.66, 4.39] [c]
Secondary endpoints:			
FEV_1 Relative change from Baseline to Day 28 of Cycle 2	N = 84 -0.62 (1.352) [b]	N = 170 2.35 (1.025) [b]	LS mean [95% CI]: 2.96 [-0.03, 5.95]
FEV_1 Relative change from Baseline to Day 28 of Cycle 3	N = 83 -0.09 (1.385) [b]	N = 166 1.98 (1.049) [b]	LS mean [95% CI]: 2.07 [-1.01, 5.15]
Respiratory domain of Cystic Fibrosis Questionnaire - Revised (CFQ-R) Change from Baseline to Day 28 of Cycle 1	N = 91 -1.31 (1.576) [b]	N = 186 1.88 (1.278) [b]	LS mean [95% CI]: 3.19 [0.05, 6.32] P = 0.046 [e]
Median time to administration of anti-pseudomonal antimicrobials	N = 93 110 days	N = 189 141 days	Hazard ratio [95% CI] [d]: 0.73 [0.53, 1.01] P = 0.040 [e]
Median time to pulmonary exacerbation	N = 93 90.5 days	N = 189 131 days	Hazard ratio [95% CI] [d]: 0.78 [0.57, 1.07] P = 0.154 [e]

CI = Confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat (all patients randomised); P = P-value; SD = standard deviation; SE = standard error; TIS = tobramycin inhalation solution.
* Note: One adolescent randomised to Quinsair 240 mg twice daily did not receive study drug.
[a] Treatment difference for Quinsair minus TIS, or Hazard ratio for Quinsair/TIS.
[b] LS Mean (SE).
[c] Non-inferiority was tested using a pre-specified, fixed non-inferiority margin of 4% at Day 28 of Cycle 1.
[d] Estimates were obtained from a Cox proportional hazards regression model.
[e] P-value determined using a log-rank test.

Patients who completed Study 209 (Core Phase) could continue in an optional Extension Phase for 3 additional cycles (i.e. 28 days of treatment with Quinsair 240 mg twice daily followed by 28 days off treatment). A total of 88 patients received at least 1 dose of Quinsair in Study 209 (Extension Phase), 32 of these had received TIS and 56 of these had received Quinsair in the Core Phase. During the Extension Phase, the LS Mean change for FEV_1 percent predicted ranged between 4.83% to 1.46% across the 3 additional treatment cycles. For the subgroup of patients who received TIS during the Core Phase and switched to Quinsair in the Extension Phase, the improvement in FEV_1 percent predicted was more marked on Quinsair than on TIS (LS Mean change in FEV_1 percent predicted on TIS ranged between 0.97% to 3.60% across Cycles 1 to 3 and between 4.00% to 6.91% across Cycles 4 to 6 on Quinsair). For the subgroup of patients who received Quinsair throughout the Core and Extension Phases (i.e. Cycles 1 to 6), the LS Mean change in FEV_1 percent predicted ranged

between 3.6% to 4.6% except in Cycle 6, where it was close to baseline (-0.15%). The proportion of patients who received Quinsair throughout Study 209 Core and Extension Phases (with a highest levofloxacin MIC *P. aeruginosa* isolate exceeding 1 µg/mL) was similar at the end of treatment during Cycles 1 and 3 in the Core Phase (76.6% to 83.3%) and at the end of treatment during Cycles 4 to 6 in the Extension Phase (77.8% to 87.5%).

In the clinical studies described above, the Zirela Nebuliser System was used to administer Quinsair. *In vitro* studies using the Zirela Nebuliser System with Quinsair have demonstrated the following drug delivery characteristics: mass median aerodynamic diameter (droplet size distribution): 3.56 micrometres (1.51 geometric standard deviation); drug delivery rate: 24.86 mg/minute (4.05 standard deviation, SD) and total drug delivered: 236.1 mg (7.1 SD).

Paediatric population

In Studies 204, 207 and 209, the relative change in FEV_1 percent predicted from baseline to the end of treatment in Cycle 1 was of similar magnitude in the 51 adolescents with CF (≥ 12 to < 18 years old and weighing ≥ 30 kg) receiving Quinsair 240 mg twice daily to that in adults. Efficacy was not evaluated in the 14 children with CF (≥ 6 to < 12 years old) and 13 adolescents with CF (≥ 12 to < 17 years old) who participated in Study 206.

The European Medicines Agency has waived the obligation to submit the results of studies with Quinsair in all subsets of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The maximal plasma concentration (C_{max}) of levofloxacin following administration by inhalation occurred at approximately 0.5-1 hour post-dose.

Multiple dose administration of Quinsair 240 mg twice daily by inhalation results in levofloxacin systemic exposure approximately 50% lower than that observed following systemic administration of comparable doses (see Table 3). However, there is variability in the systemic exposures observed which means that serum levels of levofloxacin following inhalation of Quinsair may sometimes fall within the range of levels observed following systemic administration of comparable doses.

Table 3: Comparison of mean (SD) multiple dose levofloxacin pharmacokinetic parameters following Quinsair administration by inhalation to patients with CF and following oral and intravenous administration of levofloxacin to healthy adult volunteers

Pharmacokinetic parameter	**Quinsair**	**Systemic levofloxacin**	
	240 mg Inhalation BID	**500 mg Oral QD***	**500 mg IV QD***
C_{max} (µg/mL)	2.4 (1.0)	5.7 (1.4)	6.4 (0.8)
$AUC_{(0-24)}$ (µg•h/mL)	20.9 (12.5)	47.5 (6.7)	54.6 (11.1)
IV = intravenous; QD = quaque die (once a day); BID = bis in die (twice a day) * Predicted value from population PK analysis in CF patients ** Healthy males 18-53 years old			

High levofloxacin concentrations were observed in sputum following Quinsair 240 mg twice daily dosing in patients with CF. The mean post-dose sputum concentrations were approximately 500-1,900 µg/mL and were approximately 400-1,700 times higher than those observed in serum.

Distribution

Approximately 30 to 40% of levofloxacin is bound to serum protein. The mean apparent volume of distribution of levofloxacin in serum is approximately 250 L following inhalation of Quinsair 240 mg twice daily.

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose following systemic administration and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Levofloxacin is systemically absorbed following inhalation of Quinsair and eliminated similarly to levofloxacin following systemic administration. Following oral and intravenous administration, levofloxacin is eliminated relatively slowly from the plasma ($t_{½}$: 6 to 8 hours). The half-life of levofloxacin following inhalation of Quinsair is approximately 5 to 7 hours. Elimination is primarily by the renal route (> 85% of the dose following oral or intravenous administration). The mean apparent total body clearance of levofloxacin following systemic administration of a 500 mg single dose was 175 +/- 29.2 mL/min. The apparent clearance (CL/F) of levofloxacin following inhalation of Quinsair 240 mg twice daily is 31.8 +/- 22.4 L/hour.

Linearity

Following systemic administration, levofloxacin obeys linear pharmacokinetics over a range of 50 to 1,000 mg.

Patients with renal impairment

The effects of renal impairment on the pharmacokinetics of levofloxacin administered by inhalation have not been studied. However, dose adjustments were not employed in clinical studies of Quinsair which allowed for the inclusion of patients with mild to moderate renal impairment (estimated creatinine clearance ≥ 20 mL/min using the Cockcroft-Gault formula in adult patients and ≥ 20 mL/min/1.73 m^2 using the Bedside Schwartz formula in patients < 18 years old). Studies using systemic administration of levofloxacin show that the pharmacokinetics of levofloxacin are affected by renal impairment; with decreasing renal function (estimated creatinine clearance < 50 mL/min), renal elimination and clearance are decreased, and elimination half-life increased.

Therefore, doses of Quinsair do not need to be adjusted in patients with mild to moderate renal impairment. However, Quinsair is not recommended for use in patients with severe renal impairment (creatinine clearance < 20 ml/min, see section 4.2).

Patients with hepatic impairment

Pharmacokinetic studies with Quinsair in patients with hepatic impairment have not been conducted. Due to the limited extent of levofloxacin metabolism in the liver, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Paediatric population

The safety and efficacy of Quinsair in children aged < 18 years old have not yet been established (see section 4.2).

The pharmacokinetics of levofloxacin following inhalation of Quinsair 240 mg twice daily were investigated in paediatric patients with CF aged 12 years and older and weighing ≥ 30 kg. A

population PK model based on sparse sampling determined that levofloxacin serum concentrations were comparable between paediatric and adult patients following 28 days of treatment. Higher sputum concentrations were observed in adults compared to paediatric patients in Study 207; similar sputum concentrations were observed in adult and paediatric patients in Study 209.

In addition, the pharmacokinetics of weight-based doses of levofloxacin administered by inhalation once daily for 14 days in paediatric patients with CF (≥ 6 to < 12 years old, n = 14 and ≥ 12 to < 17 years old, n = 13) were evaluated in Study 206. Patients weighing 22 to 30 kg received 180 mg levofloxacin/day and patients weighing > 30 kg received 240 mg levofloxacin/day. The weight-based dosing scheme resulted in consistent serum and sputum PK exposure across the range of ages (7 to 16 years old) and weights (22 to 61 kg) observed in the study. Serum PK exposures were similar when comparing children receiving the weight-based regimen and adults receiving Quinsair 240 mg once daily. Sputum PK exposure in children aged 7 to 16 years old was approximately one-third of adult exposure.

Elderly patients (≥ 65 years old)

The pharmacokinetics of levofloxacin administered by inhalation have not been studied in the elderly. Following systemic administration, there were no significant differences in levofloxacin pharmacokinetics between young and elderly subjects except those associated with age-related decreases in creatinine clearance.

Gender

Population pharmacokinetic analysis results showed no differences in systemic exposure of levofloxacin due to gender following administration of Quinsair.

Race

The effects of race on the pharmacokinetics of levofloxacin administered by inhalation have not been studied. Following systemic administration, the effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Fluoroquinolones have been shown to cause arthropathy in weight-bearing joints of immature animals. In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells *in vitro*. These effects can be attributed to inhibition of topoisomerase II. *In vivo* tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential. Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay. It reduced tumour development in a photocarcinogenicity study.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

Non-clinical studies conducted with levofloxacin using the inhalation route revealed no special hazard for humans based on conventional studies of safety pharmacology (respiratory), single dose toxicity and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium chloride hexahydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

3 mL, low density polyethylene ampoule.

Quinsair is supplied as 28-day pack (containing an inner carton box of 56 (14 sachets of 4) ampoules) or as 4-day pack (containing 8 (2 sachets of 4) ampoules). The outer carton box also contains one Zirela Nebuliser Handset packaged in its own carton box with the Manufacturer's Instruction for Use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Once an ampoule is opened, the contents should be used immediately. Any unused product must be discarded.

Quinsair is administered by inhalation over a 5-minute period using a Quinsair specific Zirela Nebuliser Handset and Zirela Aerosol Head connected to an eBase Controller or an eFlow rapid Control Unit (see section 4.2). Quinsair should not be used with any other type of handset or aerosol head.

Basic instructions for use are given below. More detailed instructions are available in the Package Leaflet and device Manufacturer’s Instructions for Use.

Squeeze all of the contents of one ampoule into the medicine reservoir of the Zirela Nebuliser Handset. Close the medicine reservoir by aligning the tabs of the medicine cap with the slots of the reservoir. Press down and turn the cap clockwise as far as it will go. Sit the patient in a relaxed, upright position. Holding the handset level, press and hold the on/off button on the controller for a few seconds. The controller will ‘beep’ once and the status light will turn green. After a few seconds, an aerosol mist will begin to flow into the aerosol chamber of the Zirela Nebuliser Handset. Keeping the handset level, place the mouthpiece in the patient’s mouth making sure their lips are closed around it. Ask the patient to inhale and exhale through the mouthpiece until the treatment is finished. When the

treatment is complete, the controller will ‘beep’ twice. Disconnect the controller and dismantle the Zirela Nebuliser Handset for cleaning and disinfection.

Do not put other medicinal products into the Zirela Nebuliser Handset.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/973/001
EU/1/14/973/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 March 2015
Date of latest renewal: 13 February 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Adare Pharmaceuticals S.r.l.
Via Martin Luther King, 13
20060 Pessano con Bornago (MI)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To conduct a non-interventional post-authorisation safety study in a registry of patients with cystic fibrosis to investigate the long-term safety profile of Quinsair in normal clinical practice in the European Union.	Cumulative intermediate analyses – annually. Final study report – by September 2023.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON BOX CONTAINING INNER CARTON BOX (CONTAINING 56 (14 SACHETS OF 4) AMPOULES) OR 8 (2 SACHETS OF 4) AMPOULES PLUS ONE "ZIRELA" NEBULISER HANDSET

1. NAME OF THE MEDICINAL PRODUCT

Quinsair 240 mg nebuliser solution
levofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of nebuliser solution contains levofloxacin hemihydrate equivalent to 100 mg of levofloxacin. Each ampoule contains 240 mg of levofloxacin.

3. LIST OF EXCIPIENTS

magnesium chloride hexahydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution

56 (14 sachets of 4) ampoules
8 (2 sachets of 4) ampoules

This pack also contains one Zirela Nebuliser Handset.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

For single use only. Once opened, use immediately.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/973/001 56 (14 sachets of 4) ampoules
EU/1/14/973/002 8 (2 sachets of 4) ampoules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quinsair

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON BOX CONTAINING 56 (14 SACHETS OF 4) AMPOULES

1. NAME OF THE MEDICINAL PRODUCT

Quinsair 240 mg nebuliser solution
levofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of nebuliser solution contains levofloxacin hemihydrate equivalent to 100 mg of levofloxacin. Each ampoule contains 240 mg of levofloxacin.

3. LIST OF EXCIPIENTS

magnesium chloride hexahydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution

56 (14 sachets of 4) ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

For single use only. Once opened, use immediately.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/973/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quinsair

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SACHET CONTAINING 4 AMPOULES

1. NAME OF THE MEDICINAL PRODUCT

Quinsair 240 mg nebuliser solution
levofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of nebuliser solution contains levofloxacin hemihydrate equivalent to 100 mg of levofloxacin. Each ampoule contains 240 mg of levofloxacin.

3. LIST OF EXCIPIENTS

magnesium chloride hexahydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution

4 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

For single use only. Once opened, use immediately.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Lot/EXP: See on the back

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/973/001
EU/1/14/973/002

13. BATCH NUMBER

Lot

Lot/EXP: See on the back

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quinsair 240 mg nebuliser solution
levofloxacin
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Quinsair 240 mg nebuliser solution
levofloxacin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Quinsair is and what it is used for

Quinsair contains an antibiotic medicine called levofloxacin. It belongs to the group of antibiotics called fluoroquinolones.

Quinsair is used to treat **lung infections** caused by *Pseudomonas aeruginosa* in adults with **cystic fibrosis**. It is an antibiotic medicine that is breathed (inhaled) directly into the lungs where it kills the bacteria causing the infection. This helps to improve breathing in people with cystic fibrosis.

2. What you need to know before you use Quinsair

Do not use Quinsair:
- if you are **allergic** to **levofloxacin**, to any other **quinolone antibiotics**, such as moxifloxacin, ciprofloxacin or ofloxacin, or to any of the other ingredients of this medicine (listed in section 6)
- if you have ever had a problem with your tendons (**inflammation** of a **tendon** or a **ruptured tendon**) during treatment with a **quinolone or fluoroquinolone antibiotic**
- if you suffer from **epilepsy**
- if you are **pregnant** or **breast-feeding**

Warnings and precautions

Before taking this medicine
You should not take fluoroquinolone/quinolone antibacterial medicines, including Quinsair, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

When taking this medicine
Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of Quinsair therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking Quinsair, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

Tell your doctor before using Quinsair

if you have or have ever had any of the following:

- Prolonged, disabling and potentially irreversible serious side effects
  Fluoroquinolone/quinolone antibacterial medicines, including Quinsair, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders.
  If you experience any of these side effects after taking Quinsair, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class.

- Severe kidney problems.

- A severe allergic reaction. Symptoms are listed in section 4.

- Severe skin reactions
  If you are treated with Quinsair, you may have a severe skin reaction such as blistering or lesions. Tell your doctor if you notice any skin reactions after using Quinsair.

- Liver problems. Symptoms are listed in section 4.

- Heart rhythm abnormalities
  Quinsair can cause changes to your heart rhythm, especially if you are taking any medicines to treat heart problems or low levels of potassium or magnesium in the blood. Women who take these types of medicines may be more likely to be affected. If you experience palpitations or an irregular heart beat whilst using Quinsair you should tell your doctor immediately.

- Seizures and convulsions
  Quinolone antibiotics, including Quinsair, may cause seizures or convulsions (fits). If this happens, stop using Quinsair and contact your doctor immediately.

- Depression or mental health problems.

- Nerve damage
  You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking Quinsair and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

- A disease causing muscle weakness and fatigue called myasthenia gravis.

- Inflammation of a tendon causing pain, stiffness and/or swelling in the joints (tendonitis).

- If you have experienced difficulty in breathing after receiving Quinsair, which can range from mild to severe (bronchospasm).

- Coughing up blood or blood-stained mucus from the airways.

- Glucose-6-phosphate dehydrogensae deficiency
  Quinolone antibiotics, such as Quinsair, can cause patients with glucose-6-phosphate dehydrogenase deficiency (a rare hereditary disease) to be prone to blood complications leading to a sudden rise in body temperature, yellowing of the skin and mucous membranes, dark coloured urine, paleness, tiredness, heavy, fast breathing and a weak, rapid pulse. Talk to your doctor if you have any questions about this.

- Diabetes
  Quinolone antibiotics, including Quinsair, may cause levels of glucose in the blood to be either too high or too low. If you are diabetic, you should monitor your blood glucose levels carefully.

- Diarrhoea
  You may develop diarrhoea during or after your treatment with Quinsair. If this becomes severe or persistent, or you notice blood in your stools, you should stop using Quinsair immediately and talk to your doctor. Do not take any medicines to treat your diarrhoea without first checking with your doctor.

- Resistance to antibiotics
  Bacteria can become resistant to treatment with an antibiotic over time. This means that Quinsair should not be used to prevent lung infections. It should only be used to treat lung infections caused by *Pseudomonas aeruginosa.* Talk to your doctor if you have any concerns or questions about this.

- Superinfections
  Sometimes lengthy treatment with antibiotics can mean that you get another infection caused by other bacteria which are not affected by the antibiotic (superinfection). Talk to your doctor if you have any concerns or questions about this and using Quinsair.

- Vision problems
  If you notice any changes in your eyesight or any other problems with your eyes whilst using Quinsair, contact an eye specialist immediately.

- Photosensitivity
  Quinsair may make your skin become more sensitive to sunlight. You should avoid prolonged exposure to sunlight or strong sunlight and should not use sunbeds or any other UV lamps whilst using Quinsair and for 48 hours after stopping treatment.

- False test results
  Certain tests (e.g. to confirm tuberculosis or screening for strong painkillers) may give false results whilst you are being treated with Quinsair.

- if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).

- if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).

- if you have been diagnosed with leaking heart valves (heart valve regurgitation).

- if you have a family history of aortic aneurysm or aortic dissection or congenital heart valve disease, or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or Ehlers-Danlos syndrome, Turner syndrome, Sjögren's syndrome [an inflammatory autoimmune disease], or vascular disorders such as Takayasu arteritis, giant cell

arteritis, Behcet's disease, high blood pressure, or known atherosclerosis, rheumatoid arthritis [a disease of the joints,] or endocarditis [an infection of the heart]).

If you feel sudden, severe pain in your abdomen, chest or back, which can be symptoms of aortic aneurysm and dissection, go immediately to an emergency room. Your risk may be increased if you are being treated with systemic corticosteroids.

If you start experiencing a rapid onset of shortness of breath, especially when you lie down flat in your bed, or you notice swelling of your ankles, feet or abdomen, or a new onset of heart palpitations (sensation of rapid or irregular heartbeat), you should inform a doctor immediately.

Children and adolescents
Quinsair should not be given to children and adolescents less than 18 years old as there is not enough information about its use in this age group.

Other medicines and Quinsair
Tell your doctor or a pharmacist if you are taking, have recently taken or might take any other medicines. These medicines may interfere with the effects of Quinsair.

Tell your doctor if you are taking any of the following medicines:
- Vitamin K antagonists such as **warfarin** (used to prevent blood clots). Taking these medicines with Quinsair may lead to an increase in bleeding. Your doctor may need to give you regular blood tests to check how well your blood can clot.

- **Theophylline** (used to treat breathing problems) or non-steroidal anti-inflammatory medicines (NSAIDs) such as **fenbufen**, **acetylsalicylic acid** (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting) or **ibuprofen**. Taking Quinsair at the same time as these medicines could increase your risk of a fit (seizure).

- Medicines such as **probenecid** (used to prevent gout) or **cimetidine** (used to treat ulcers). Taking Quinsair at the same time as these medicines could affect how your kidneys deal with the medicine which is particularly important if you suffer from kidney problems.

- **Ciclosporin** (used after organ transplants) or **medicines that affect your heart beat** (such as antiarrhythmics, tricyclic antidepressants, macrolide antibiotics or antipsychotics). Quinsair can interfere with the effects of these medicines. Your doctor will explain more.

Pregnancy and breast-feeding
Quinsair must not be used whilst pregnant or breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
Quinsair may make you feel dizzy, tired or weak, or cause problems with your eyesight. If this happens to you, do not drive or use any tools or machines.

3. How to use Quinsair

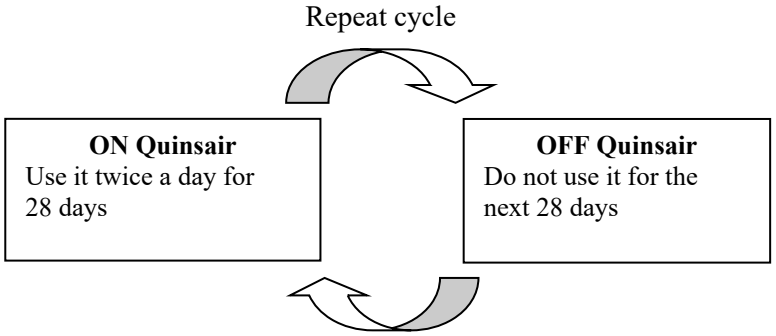
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How much do I use?
Inhale the contents of **one ampoule (240 mg) twice a day using the Zirela Nebuliser System**. It takes about 5 minutes to inhale the medicine using the nebuliser.

When do I use it?
Inhaling Quinsair at the same time each day will help you remember when to take your medicine.
Inhale your medicine as follows:
- 1 ampoule in the morning using the Zirela Nebuliser
- 1 ampoule in the evening using the Zirela Nebuliser

It is best to leave close to 12 hours between your doses.

How long do I use it for?
You use Quinsair every day for 28 days, then take a 28-day break, during which you do not inhale any Quinsair. You then start another treatment course.
It is important that you keep using the medicine twice a day during your 28 days on treatment and that you keep to the 28-days on, 28-days off cycle for as long as your doctor tells you to.



If you experience breathing difficulties when you use Quinsair what additional medicine may your doctor prescribe for you?
If you experience breathing difficulties after using Quinsair, your doctor may prescribe you an inhaler containing a bronchodilator medicine (e.g. salbutamol). Inhale this medicine at least 15 minutes or up to 4 hours before your next dose of Quinsair.

What if I am using several different inhalers and other therapies for cystic fibrosis?
If you are using several different inhaled treatments and other therapies for cystic fibrosis, it is recommended that you use your medicines in the following order:
1st Bronchodilators
2nd Dornase alfa
3rd Airway clearance techniques
4th Quinsair
5th Inhaled steroids

How to use it
Quinsair should be taken by inhalation using a **Zirela Nebuliser Handset** (including a Zirela Aerosol Head). This should be connected to either an eBase Controller or an eFlow rapid Control Unit.

Important information to know before you start
- Each ampoule is **for single use only. Once an ampoule is opened, the contents should be used immediately.**
- Do not use Quinsair if you notice that the sealed foil sachet or ampoules have been tampered with.
- Do not use Quinsair if you notice that it is cloudy or there are particles in the solution.
- **Do not mix Quinsair with any other medicines** in the Zirela Nebuliser Handset.
- Do not put any medicines other than Quinsair in the Zirela Nebuliser Handset.
- Do not try to inhale Quinsair using any other type of nebuliser handset.
- Check that your Zirela Nebuliser System works properly before starting your treatment.
- Do not swallow the liquid in the ampoule.

Carefully read the Manufacturer's Instructions for Use, provided with your Zirela Nebuliser Handset.

How do I prepare my Nebuliser System to inhale the medicine?
Keep the Zirela Instructions for Use in a safe place as they give full details on assembling the device.

1) **Make sure that the Zirela Nebuliser Handset** is on a flat and stable surface.

2) **Squeeze all of the contents of one ampoule** into the medicine reservoir of the Zirela Nebuliser Handset (Figure 1). Ensure that you completely empty the ampoule, gently tapping it against the side of the reservoir if necessary.

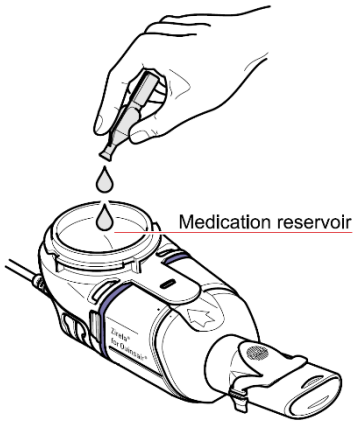


Figure 1

3) **Close the medicine reservoir** by aligning the tabs of the medicine cap with the slots of the reservoir (a). Press down and turn the cap clockwise as far as it will go (b, Figure 2).

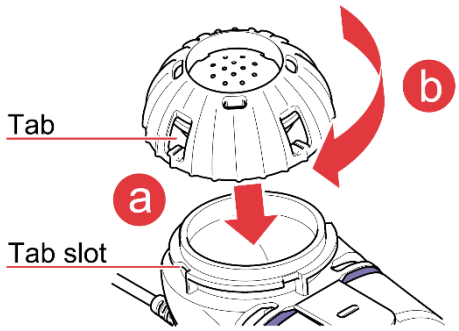


Figure 2

How do I use the Zirela Nebuliser System?

1) **When you start your treatment**, sit in a relaxed, upright position.

2) **Hold the handset level**, press and hold the on/off button on the controller for a few seconds. You will hear one ‘beep’ and the status light will turn green.

3) **After a few seconds, an aerosol mist will begin to flow** into the aerosol chamber of the Zirela Nebuliser Handset. If aerosol mist does not begin to flow, please refer to the Zirela Manufacturer’s Instructions for Use for help.

4) **Keeping the handset level,** place the mouthpiece in your mouth and close your lips around it (Figure 3).

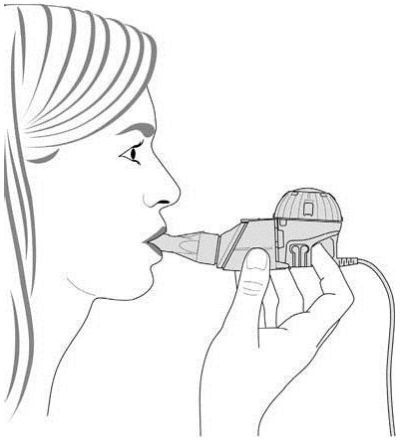


Figure 3

5) **Breathe normally** (inhale and exhale) through the mouthpiece. Try not to breathe through your nose. Continue to inhale and exhale comfortably until the treatment is finished. It takes about 5 minutes to inhale the medicine using the nebuliser.

6) **When all of the medicine has been delivered**, you will hear two 'beeps', which means the treatment is complete.

7) **Once complete, open the medicine cap** to ensure all of the medicine has been used. A few drops of medicine may remain at the bottom of the reservoir at the end of treatment. This is ok. However if there are more than a few drops left, replace the medicine cap and restart treatment, from step 1.

8) **Once treatment is complete**, disconnect the controller and take apart the Zirela Nebuliser Handset for cleaning and disinfecting. The Manufacturer's Instructions for Use will give full details on cleaning and disinfecting.

What if I need to stop my treatment before I've finished?
If for any reason you must stop the treatment before it's finished, press and hold the controller's on/off button for one second. After it has completely turned itself off and when you are ready to restart, press and hold the on/off button for one second again. Treatment will restart. You must inhale and exhale through the mouthpiece as before.

How and when do I replace the Zirela Nebuliser Handset?
One nebuliser handset should be used for one 28-day treatment course. Please refer to the Manufacturer's Instructions for Use for cleaning and storage advice.

If you use more Quinsair than you should
If you have used more Quinsair than you should, **tell your doctor as soon as possible**. You may experience symptoms like irregular heart beat, which needs to be checked by your doctor. If the contents of the ampoule are swallowed, don't worry but tell your doctor as soon as possible.

If you forget to use Quinsair
If you forget a dose, use it as soon as you remember as long as there is an 8-hour interval before inhaling the next dose. However if it is nearly the time for your next dose, skip the missed dose.

Do not inhale the contents of more than one ampoule to make up for a missed dose.

If you stop using Quinsair
Do not stop using Quinsair without first talking to your doctor as your lung infection may worsen.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious
Get **urgent medical treatment immediately** if you notice a **severe allergic reaction** after inhaling Quinsair. Symptoms include:
- General itching and feeling of heat – especially affecting the scalp, mouth, throat, palms or soles of your feet
- Severe wheezing, or noisy or difficult breathing
- Severe hives/nettle rash
- Swelling of the lips, face, throat or tongue
- Pale or greyish skin colour
- A fast heart beat
- Faintness or passing out

Stop using Quinsair and tell your doctor immediately:
- if you experience **pain, stiffness and/or swelling in your joints**
- if you develop **problems with your liver**. Symptoms include:
  - Loss of appetite
  - Yellowing of the skin and eyes (jaundice)
  - Dark coloured urine
  - Itching
  - Tenderness (pain) around the stomach (abdomen)

Other side effects can include:
Very common: may affect more than 1 in 10 people
- Cough
- Abnormal sense of taste
- Tiredness, weakness and lower tolerance to exercise
- Loss of appetite
- Shortness of breath
- Changes in the amount and thickness of mucus/phlegm
- Coughing up blood
- Decreased amount of air that can be breathed out in one second (decreased FEV_1 test)

Common: may affect up to 1 in 10 people
- Fungal infection around vagina
- Insomnia or difficulty sleeping
- Headache
- Dizziness
- Ringing or noise in the ears (tinnitus)
- Change to the voice
- Feeling and being sick
- Abdominal pain
- Diarrhoea
- Constipation
- Rash
- Joint or muscle pain
- Fever
- Abnormal blood test results (increased levels of certain liver enzymes or bilirubin in the blood, and decreased kidney function test)
- Decreased lung function test
- Increased or decreased amount of sugar (glucose) in the blood

- Abnormal breathing sounds

Uncommon: may affect up to 1 in 100 people
- Fungal infection of the mouth
- Low numbers of red cells in the blood (anaemia) or the cells in the blood that help it clot (platelets)
- Low or high numbers of white cells in the blood
- Feeling anxious, restless or agitated and/or depressed
- Reduced sense of smell
- Feeling sleepy
- Changes in eyesight
- Loss of hearing
- Increased heart beat
- Difficulty in breathing
- Retching
- Indigestion
- Passing wind
- Hives/nettle rash and itching
- Chest wall pain
- Kidney failure
- Changes in heart rhythm
- Pain, burning, tingling, numbness and/or weakness in the limbs (neuropathy)

The following side effects have also been reported after taking tablets or an intravenous infusion containing levofloxacin, so they might possibly occur after using Quinsair:

Uncommon: may affect up to 1 in 100 people
- Feeling confused or nervous
- Shaking
- Sensation of dizziness, spinning or falling over (vertigo)
- Excessive sweating

Rare: may affect up to 1 in 1,000 people
- Hallucinations and/or feeling paranoid
- Feeling agitated
- Unusual dreams or nightmares
- Convulsions (fits)
- Tingling sensation (pins and needles) and/or numbness
- Palpitations
- Low blood pressure
- Muscle weakness
- Syndrome associated with impaired water excretion and low levels of sodium (SIADH)
- Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms)
- Sharply demarcated, erythematous patches with/without blistering

Not known: frequency cannot be estimated from the available data
- Low numbers of all types of cells in the blood
- Diabetic coma
- Severe mental problems (which in very rare cases may lead to self-harm)
- Pain, burning, tingling, numbness and/or weakness in the limbs (neuropathy)
- Involuntary muscle movements, twitching or spasms
- Fainting
- Severe throbbing headaches with loss of eyesight
- Temporary loss of vision
- Rapid or abnormal heart beat

- Inflammation of the lung
- Severe skin reactions such as painful blistering or lesions possibly in the mouth, nose or vagina
- Increased sensitivity of the skin to sunlight or UV light (sunbeds or other UV lamps)
- Inflammation of the blood vessels
- Inflammation of the mouth or lips
- Rapid breakdown of muscles
- Inflammation of a tendon or a broken tendon
- Pain including pain in the back, chest, arms and legs and arms

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Cases of an enlargement and weakening of the aortic wall or a tear in the aortic wall (aneurysms and dissections), which may rupture and may be fatal, and of leaking heart valves have been reported in patients receiving fluoroquinolones. See also section 2.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Quinsair

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the ampoule, the foil sachet and the boxes after EXP. The expiry date refers to the last day of that month.

Each ampoule is for single use only. Once an ampoule is opened, the contents should be used immediately. Any unused product must be thrown away. Replace any unused, unopened ampoules from the strip back into the sachet to protect them from light.

Store in the original package in order to protect from light. This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Quinsair contains
- The active substance is levofloxacin. One ampoule contains levofloxacin hemihydrate equivalent to 240 mg of levofloxacin.
- The other ingredients are magnesium chloride hexahydrate and water for injections.

What Quinsair looks like and contents of the pack
Quinsair is a clear, pale yellow nebuliser solution. The medicine comes in small 3 mL plastic ampoules. Four ampoules are sealed in a foil sachet.

Quinsair is supplied as 28-day pack (containing one box of 56 (14 sachets of 4) ampoules) or as 4-day pack (containing 8 (2 sachets of 4) ampoules) and one box holding a Zirela Nebuliser Handset with the Manufacturer's Instructions for Use.
Not all pack sizes may be marketed.

The ampoule is labelled in English only. The information that appears on the ampoule is:

On the front of the ampoule tail
Quinsair 240 mg
Nebuliser Solution
Levofloxacin
Inhalation use 2.4 mL

In the "crimped area" on either side of the ampoule tail
Lot
EXP

Marketing Authorisation Holder
Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

Manufacturer
Adare Pharmaceuticals S.r.l.
Via Martin Luther King, 13
20060 Pessano con Bornago (MI)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.