SUMMARY OF PRODUCT CHARACTERISTICS

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.

4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to

all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection;
- other first-line antibiotics are contraindicated in an individual patient;
- other first-line antibiotics have caused side effects requiring treatment to be stopped;
- treatment with other first-line antibiotics has failed.

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).

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).

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. 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, so that symptoms can be

appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

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 rupture (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 rupture 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.

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*

System organ class	Very common	Common	Uncommon
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*

System organ class	Very common	Common	Uncommon
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	
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*

System organ class	Very common	Common	Uncommon
[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 rupture (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)	

System organ class	Uncommon	Rare	Not known
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
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

System organ class	Uncommon	Rare	Not known
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, Tendon rupture, Tendinitis	Rhabdomyolysis, 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] 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, fatigue, psychiatric symptoms, memory impairment, 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). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (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:
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5.1 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

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

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M22 5LG

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