

**National Institute for Health and Care Excellence**

**Evidence review**

# **Chronic pseudomonas lung infection in cystic fibrosis: levofloxacin nebuliser solution**

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Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence summary was up-to-date in September 2016. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## **Key points from the evidence**

### **Summary**

In people with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection previously treated with nebulised tobramycin, nebulised levofloxacin 240 mg twice daily was shown to be non-inferior but not superior to nebulised tobramycin 300 mg twice daily in terms of lung function as measured by FEV<sub>1</sub>. When nebulised levofloxacin was compared with placebo no difference was found for time to exacerbation of cystic fibrosis lung disease. The adverse effects associated with oral and intravenous administration of levofloxacin are also a potential risk with the nebulised route of administration. There are limited data on long-term use. Nebulised levofloxacin costs the same as nebulised aztreonam, but it is more expensive than colistimethate sodium and tobramycin in either the nebulised or dry powder inhalation formulations.

**Regulatory status:** Levofloxacin nebuliser solution ([Quinsair](#)) was launched in the UK in June 2016 and is the first nebulised fluoroquinolone antibiotic to be licensed for the management of chronic pulmonary infections due to

*P. aeruginosa* in adult patients with cystic fibrosis. Levofloxacin nebuliser solution is not licensed for use in children and young people under 18 years.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>No statistically significant difference between nebulised levofloxacin 240 mg twice daily and placebo for time to first exacerbation of cystic fibrosis lung disease (1 RCT; n=330; 1 cycle [28 days treatment and 28 days follow-up]).</li> <li>Non-inferior but not superior to nebulised tobramycin for relative change in FEV<sub>1</sub> percent predicted (1 open-label randomised study; n=282; 3 cycles of treatment but primary FEV<sub>1</sub> outcome from baseline to 28 days).</li> <li>Difference of +1.31% for least squares (LS) mean change in FEV<sub>1</sub> percent predicted and -0.63 for LS mean change in <i>P. aeruginosa</i> sputum density (log<sub>10</sub> CFUs per gram) compared with placebo (1 RCT; n=330; 1 cycle of treatment), the clinical significance of these differences is unclear.</li> </ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>Serum concentrations of nebulised levofloxacin were on average approximately 50% of that seen with oral and intravenous routes of administration at usual doses. Therefore all of the possible adverse effects associated with oral or intravenous administration of levofloxacin are also a potential risk with the nebulised formulation.</li> <li>The European Public Assessment Report (EPAR) for <a href="#">Quinsair</a> concluded that the long-term safety profile of nebulised levofloxacin in adults remains unclear. Additionally the EPAR concluded that use in children and young people under 18 could not be recommended due to safety concerns.</li> </ul>
<p><b>Patient factors</b></p> <ul style="list-style-type: none"> <li>Levofloxacin nebuliser solution is nebulised over 5 minutes twice a day.</li> <li>The EPAR reports that nebulised levofloxacin may irritate the upper and lower airways.</li> <li>Dysgeusia (taste disturbance) was a common adverse effect in clinical trials (reported in 32.5% and 25.3% of participants taking nebulised levofloxacin compared with no participants taking placebo or nebulised tobramycin; 1 RCT and 1 open label randomised study; n=330 and 282 respectively).</li> </ul>	<p><b>Resource implications</b></p> <ul style="list-style-type: none"> <li>The cost of 28 days treatment with nebulised levofloxacin is £2181.53. This is the same as the cost of 28 days treatment with nebulised aztreonam.</li> <li>Nebulised levofloxacin is more expensive than colistimethate sodium and tobramycin (cost of 28 days treatment ranging from approximately £100 to £1800 depending on preparation used) [All costs based on listed prices in <a href="#">MIMS</a> and the <a href="#">Drug Tariff</a>].</li> </ul>

### ***Introduction and current guidance***

The lungs of people with cystic fibrosis can become infected by bacteria (most commonly *P. aeruginosa*); bacterial infection is rarely eradicated once chronic infection has developed. The [NHS England clinical commissioning policy on](#)

[inhaled therapy for adults and children with cystic fibrosis](#) (published January 2015) details the clinical criteria under which NHS England will routinely fund inhaled therapies for people with cystic fibrosis. The policy recommends a stepwise approach to treatment for chronic *P. aeruginosa* infection with colistimethate sodium first line when pulmonary function is normal but chronic *P. aeruginosa* infection is evident. If there is decline in lung function or exacerbations requiring intravenous antibiotics as further described and specified in the policy, tobramycin (which may be rotated on a monthly basis with colistimethate sodium) is recommended second line and then aztreonam (which may be rotated with colistimethate sodium or tobramycin) is recommended third line. NICE has issued technology appraisal guidance on [colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#). A NICE guideline on [diagnosis and management of cystic fibrosis](#) is in development. The expected date of publication is October 2017.

[Full text of Introduction and current guidance.](#)

### **Product overview**

Levofloxacin nebuliser solution ([Quinsair](#)) is licensed for the management of chronic pulmonary infections due to *P. aeruginosa* in adult patients with cystic fibrosis. The recommended dosage is 240 mg (one ampoule) administered by inhalation twice daily over a 5 minute period. It 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 clinician considers that the patient is obtaining clinical benefit.

[Full text of Product overview.](#)

### **Evidence review**

Nebulised levofloxacin has been compared with placebo over 1 cycle of treatment (28 days treatment and 28 days follow-up) in a double-[blind randomised controlled trial](#) (RCT) [[Flume et al. 2015](#); n=330] and with nebulised tobramycin over 3 cycles of treatment in an open-label non-inferiority randomised study ([Elborn et al. 2015](#); n=282). The population in

both studies was aged over 12 with a documented diagnosis of cystic fibrosis, a forced expiratory volume in 1 second (FEV<sub>1</sub>) between 25% and 85% predicted and a chronic airways infection with *P. aeruginosa*. Over the previous 12 months participants had received at least three 28-day courses (or a total of 84 days) of either inhaled antibiotics in Flume et al. (2015) or inhaled tobramycin in Elborn et al. (2015). The majority of people in the 2 studies were aged over 18 (85% and 86%) and the mean ages in the studies were 28 and 29.

- In [Flume et al. 2015](#) there was no statistically significant difference for the primary outcome of time to first exacerbation of cystic fibrosis lung disease (as defined in the study, see main section [evidence review](#) for more details) compared with placebo (median of 51.5 days with levofloxacin compared with 58.0 days with placebo; [hazard ratio](#) [HR] 1.33; 95% [confidence interval](#) [CI] 0.96 to 1.84). There was also no statistically significant difference between levofloxacin and placebo for time to administration of antipseudomonal antibiotics other than the study drug (HR 0.85; 95% CI 0.61 to 1.18).
- A treatment difference was found between nebulised levofloxacin and placebo for the secondary outcomes of mean change from baseline to day 28 in FEV<sub>1</sub> percent predicted (LS mean treatment difference 1.31%; 95% CI 0.27 to 2.34) and *P. aeruginosa* log<sub>10</sub> colony forming units (CFUs) per gram sputum density (LS mean treatment difference -0.63; 95% CI -0.95 to -0.30). However, the clinical significance of these treatment differences is unclear.
- In [Elborn et al. 2015](#) nebulised levofloxacin was shown to be non-inferior but not superior to nebulised tobramycin for relative change in FEV<sub>1</sub> percent predicted from baseline to day 28 with a predefined non-inferiority margin of a lower 95% CI greater than -4%. Mean FEV<sub>1</sub> percent predicted changed from 54.8% to 56.0% in the levofloxacin group and from 53.2% to 53.3% in the tobramycin group (LS mean treatment difference in relative change 1.86%; 95% CI -0.66 to 4.39; p=0.15). The [EPAR for Quinsair](#) commented that a comparison between tobramycin and levofloxacin in people naive to levofloxacin but not tobramycin could be biased in favour of

levofloxacin. There was no statistical significant difference between the 2 groups for time to exacerbation (HR 0.78; 95% CI 0.57 to 1.07; p=0.15).

- The EPAR reported that serum concentrations of levofloxacin from nebulised administration were on average approximately 50% of that seen with oral and intravenous routes of administration at usual doses. This is reflected in the summary of product characteristics ([SPC: Quinsair](#)) which includes warnings and precautions for use associated with systemic administration of levofloxacin and the fluoroquinolone class of antibiotics, as well as those specific for inhaled administration (such as bronchospasm).
- The EPAR further reports that there were relatively few fluoroquinolone class associated adverse events in the studies but that hepatotoxicity and possibly tendon and cartilage disorders and peripheral neuropathy are potential risks of treatment. There are limited long-term data and the EPAR concluded that the long-term safety profile of nebulised levofloxacin in adults remains unclear; further safety studies including safety studies in children and young people under 18 are planned.
- The manufacturers had originally submitted a license application which included children and young people aged from 12 years and 30 kg body weight. The EPAR concluded that currently use could not be recommended for people aged less than 18 years due to safety concerns such as the lack of long-term data, predicted serum concentrations after nebulisation and the additional potential risk of adverse effects on cartilage in this age group. On this basis, the manufacturers withdrew the license application for this age group.
- Levofloxacin nebuliser solution is contraindicated in people who have a hypersensitivity to levofloxacin or any other fluoroquinolone antibiotic, people with a history of tendon disorders related to fluoroquinolones, people with epilepsy and pregnant or breast feeding women (SPC: [Quinsair](#)). The SPC also states that use is not recommended in people with severe renal impairment (creatinine clearance less than 20 ml/min). The SPC reports that the most frequently reported adverse reactions in studies were cough (54%), dysgeusia (30%) and fatigue or asthenia (25%). See

the [SPC](#) for further information on contraindications, warnings and precautions for use, potential interactions and adverse effects of nebulised levofloxacin.

[Full text of Evidence review.](#)

## **Context**

Inhaled antibiotic treatments currently licensed in the UK for the management of chronic pulmonary infections due to *P. aeruginosa* in people with cystic fibrosis include: colistimethate sodium, a polymyxin antibiotic ([Promixin powder for nebuliser solution](#), [colomycin powder for solution for injection, infusion or inhalation](#) and [Colobreathe](#) a dry powder for inhalation); tobramycin, an aminoglycoside antibiotic ([Bramitob nebuliser solution](#), [Tobi nebuliser solution](#) and [Tobi podhaler](#) a dry powder for inhalation); aztreonam, a beta-lactam antibiotic ([Cayston powder and solvent for nebuliser solution](#)); and levofloxacin, a fluoroquinolone antibiotic ([Quinsair](#) nebuliser solution). Levofloxacin nebuliser solution is not licensed for use in children and young people under 18. The other available inhaled preparations are licensed for use in children, however the age from which they are licensed varies between the individual products; please see the individual SPCs for further information.

[Full text of Context.](#)

## **Estimated impact for the NHS**

Levofloxacin nebuliser solution is the first nebulised fluoroquinolone antibiotic to be licensed for the management of chronic pulmonary infections due to *P. aeruginosa* in adult patients with cystic fibrosis. The EPAR for Quinsair concluded that the addition of nebulised levofloxacin to the 3 inhaled antibiotics already licensed for this indication would allow for further rotational cyclical regimens of treatments from different classes.

[Full text of Estimated impact for the NHS.](#)

<b>About this evidence summary</b>
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'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Full evidence summary

### ***Introduction and current guidance***

Cystic fibrosis is an inherited condition characterised by abnormal transport of chloride and sodium across the epithelium in all exocrine tissues. This leads to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and an increase in the salt content in sweat gland secretions. Cystic fibrosis is a progressive condition that limits life expectancy. However, prognosis is improving with the new treatments now available and around half of the current cystic fibrosis population are expected to have a life expectancy of over 38 years (NICE technology appraisal guidance:

[Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#)).

The lungs of people with cystic fibrosis can become infected by bacteria (most commonly *Pseudomonas aeruginosa*), which thrive in the altered mucus that collects in the small airways. Recurrent, intermittent infection of the airways occurs and, if bacterial infection is not controlled, chronic infection can develop. In chronic infection, bacterial micro-environments known as biofilms are formed that are difficult for immune cells and antibiotics to penetrate. Bacterial infection is rarely eradicated once chronic infection has developed (NICE technology appraisal guidance: [Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#)).

Management of *P. aeruginosa* lung infection in cystic fibrosis involves treatment with antibiotics. The aims of treatment are three fold: eradication of intermittent acute *P. aeruginosa* infections; suppression of *P. aeruginosa* infection (with long-term therapy) in patients who have become chronically infected and; treatment of acute exacerbations in patients chronically infected with *P. aeruginosa*. Treatment also aims to maintain lung function and quality of life. Treatment options include the use of inhaled antibiotics effective against *P. aeruginosa* and oral or intravenous antibiotics to eradicate initial or intermittent *P. aeruginosa* colonisation or acute exacerbations of chronic



infections (NICE technology appraisal guidance: [Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#)).

[The guideline on antibiotic treatment for cystic fibrosis](#) from the Cystic Fibrosis Trust (2009) advises that people with cystic fibrosis and chronic *P. aeruginosa* infection should be considered for regular nebulised antipseudomonal antibiotic treatment. Inhaled antibiotic treatments currently licensed in the UK for the management of chronic pulmonary infections due to *P. aeruginosa* in people with cystic fibrosis include: nebulised colistimethate sodium ([Promixin powder for nebuliser solution](#), [colomycin powder for solution for injection, infusion or inhalation](#)), colistimethate dry powder for inhalation ([Colobreathe](#)), nebulised tobramycin ([Bramitob nebuliser solution](#), [Tobi nebuliser solution](#)), tobramycin dry powder for inhalation ([Tobi podhaler](#)), nebulised aztreonam ([Cayston powder and solvent for nebuliser solution](#)) and levofloxacin nebuliser solution ([Quinsair](#)). Levofloxacin nebuliser solution is not licensed for use in children and young people under 18. The other available inhaled preparations are licensed for use in children, however the age from which they are licensed varies between the individual products; see the individual SPCs for further information.

The [NHS England clinical commissioning policy on inhaled therapy for adults and children with cystic fibrosis](#) (published January 2015) details the clinical criteria under which NHS England will routinely fund inhaled therapies (including colistimethate sodium, tobramycin and aztreonam) for people with cystic fibrosis. The policy recommends a stepwise approach to treatment for chronic *P. aeruginosa* infection. Colistimethate sodium is recommended first-line when pulmonary function is normal but chronic *P. aeruginosa* infection is evident. Tobramycin is recommended second-line if despite continued therapy and good adherence to treatment; lung function continues to decline or there is a requirement for more than 1 course of intravenous antibiotics in the preceding year. This may be prescribed in an alternative monthly regimen rotated with colistimethate sodium. Aztreonam is recommended third-line if there is further decline in lung function or exacerbations requiring intravenous

antibiotics as further described and specified in the policy. Aztreonam may be prescribed in an alternative monthly regimen rotated with either colistimethate sodium or tobramycin depending on the clinical response to those medications previously.

The European Public Assessment Report (EPAR) for [Quinsair](#) comments that there has been a change in clinical practice regarding how chronic *P. aeruginosa* infection is managed in people with cystic fibrosis. The EPAR states that it is now common practice to rotate inhaled antibiotics by cycle.

NICE has issued technology appraisal guidance on [colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#). NICE has also issued technology appraisal guidance on [mannitol dry powder for inhalation for treating cystic fibrosis](#). A NICE guideline on [diagnosis and management of cystic fibrosis](#) is in development. The expected date of publication is October 2017.

## ***Product overview***

### **Drug action**

Levofloxacin is a fluoroquinolone antibiotic.

### **Licensed therapeutic indication**

Levofloxacin nebuliser solution ([Quinsair](#)) is licensed for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents. The SPC states that the safety and efficacy of inhaled levofloxacin in children and young people aged less than 18 years of age has not yet been established. Use in children and young people younger than 18 would be off-label\*.

\*In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using nebulised levofloxacin outside its authorised indications.

## Course and cost

The recommended dosage of levofloxacin is 240 mg (one ampoule) administered by nebulisation twice daily. It 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 clinician considers that the patient is obtaining clinical benefit. The doses should be inhaled as close as possible to 12 hours apart. If a dose is missed, it should be taken as soon as the patient remembers providing that there is at least an 8 hour interval before inhaling the next dose (summary of product characteristics [SPC]: [Quinsair](#)).

Levofloxacin nebuliser solution should be administered by inhalation over a 5 minute period using the provided Zirela Nebuliser Handset. The Zirela Aerosol Head within the handset needs to be connected to an eBase Controller or an eFlow rapid Control Unit. Levofloxacin nebuliser solution should not be used with any other type of handset or aerosol head. Levofloxacin nebuliser solution comes in ready to use ampoules, which do not require re-constitution ([SPC](#)).

The SPC recommends that if acute symptomatic bronchospasm occurs after use, people may benefit from using a short-acting inhaled bronchodilator at least 15 minutes to 4 hours before subsequent doses. For patients taking multiple inhaled therapies, the SPC recommends the following order of administration:

1. bronchodilators
2. dornase alfa
3. airway clearance techniques
4. levofloxacin nebuliser solution
5. inhaled steroids.

The cost of 28 days treatment with nebulised levofloxacin is £2181.53 (based on a cost of £2181.53 for 56 × 2.4ml single use ampoules plus 1 Zirela nebuliser handset [[MIMS June 2016](#)]).

## **Evidence review**

This evidence summary discusses the [best available evidence](#) on the efficacy and safety of nebulised levofloxacin (Quinsair) for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in people with cystic fibrosis. This is a double-[blind randomised controlled trial](#) (RCT) comparing 28 days of nebulised levofloxacin with placebo ([Flume et al. 2015](#)) and an open-label randomised non-inferiority study comparing nebulised levofloxacin with nebulised tobramycin over 3 cycles of treatment ([Elborn et al. 2015](#)). An open-label non-randomised extension study to Elborn et al. (2015) is also briefly discussed in the safety section ([Elborn et al. 2016](#)). Information from these studies has been supplemented and clarified using the European Public Assessment Report (EPAR) for [Quinsair](#).

### **[Flume et al. 2015](#)**

- Design: multicentre, double-blind, placebo-controlled RCT of 1 cycle of treatment consisting of 28 days treatment and 28 days follow-up conducted in 5 countries (US, Canada, Australia, New Zealand and Israel), although the majority of participants were from the US (89%). [Allocation was concealed](#).
- Population: the study included 330 people (55% male) over 12 years (mean age 29 years; 85% were over 18 years of age) with a documented diagnosis of cystic fibrosis, a forced expiratory volume in 1 second (FEV<sub>1</sub>) between 25% and 85% predicted (mean 56.5%) and a chronic airways infection with *P. aeruginosa* who had received at least three 28 day courses (or a total of 84 days) of inhaled antibiotics over the previous 12 months, with at least a 14 day course completed within the previous 29 to 84 days. Although people who had received antipseudomonal antibiotics in the past 28 days (with the exception of maintenance oral azithromycin) were excluded from the study. Chronic *P. aeruginosa* infection was defined as a respiratory secretion culture positive for *P. aeruginosa* in the previous 12 months and a positive culture obtained at the screening visit. Participants had not smoked within the previous 28 days and had agreed

not to smoke for the duration of the study. Over the previous 12 months, participants had had a mean of 6 courses of inhaled antibiotics.

- Intervention and comparison: participants were randomised 2:1 to either levofloxacin 240 mg nebulised twice a day or 0.9% saline nebulised twice daily. All of the study drugs were delivered via a PARI investigational eFlow nebuliser. The treatments were blinded for appearance but not taste. Participants were able to continue their routine respiratory care and medications during the study. Antipseudomonal antibiotics other than the study drug were not allowed unless it was deemed necessary to treat a suspected exacerbation by the study investigator.
- Outcomes: the primary efficacy outcome was time to an exacerbation of cystic fibrosis lung disease. An exacerbation was defined by concurrently having changes in at least 4 out of the 12 respiratory signs or symptoms that make up the modified [Fuchs definition](#) (see table 1 footnote for more information), independent of an investigator decision to treat with an antibiotic. Use of the Fuchs criteria in this manner was a modification of its original use, which was to confirm a clinician's decision to treat with intravenous antibiotics for a respiratory event. The following were also defined as an exacerbation for the purposes of the primary endpoint: early discontinuation from the study, death or treatment with an antipseudomonal antibiotic for an event that did not meet the predefined criteria but was determined to be an exacerbation for the purposes of the primary endpoint by an independent, blinded, exacerbation adjudication committee. Secondary and additional outcomes included change from baseline to day 28 for: FEV<sub>1</sub> percent predicted, [cystic fibrosis questionnaire-revised](#) (CFQ-R) respiratory symptom score (a health-related quality of life measure) and sputum *P. aeruginosa* density. Efficacy outcomes were conducted for the [intention to treat](#) population (defined as all randomised participants). Safety outcomes included adverse event reporting.

**Table 1 Summary of [Flume et al. 2015](#)**

	<b>Levofloxacin 240 mg nebulised twice a day</b>	<b>0.9% saline nebulised twice a day</b>	<b>Analysis</b>
Randomised	n=220	n=110	
<b>Efficacy (ITT population)<sup>a</sup></b>	n=220	n=110	
Primary outcome: time to first exacerbation (median time in days) <sup>b,c</sup>	51.5 days percentage of participants who had an exacerbation during study: 55.5% (122/220)	58.0 days percentage of participants who had an exacerbation during study: 47.3% (52/110)	No statistical significant difference between nebulised levofloxacin and placebo for time to first exacerbation: HR 1.33; 95% CI 0.96 to 1.84
Selected secondary outcomes:			
LS mean change (SE) from baseline to day 28 in FEV <sub>1</sub> percent predicted <sup>c</sup>	Mean (SD) at baseline: 56.6% (15.7) LS mean change from baseline: 1.73% (0.471)	Mean (SD) at baseline: 56.3% (15.9) LS mean change from baseline: 0.43% (0.568)	LS mean treatment difference 1.31; 95% CI 0.27 to 2.34 <sup>d</sup>
LS mean change (SE) in <i>P. aeruginosa</i> sputum density (log <sub>10</sub> CFUs per gram) <sup>c</sup>	-0.59 (0.139)	0.04 (0.170)	LS mean treatment difference -0.63; 95% CI -0.95 to -0.30 <sup>d</sup>
LS mean change (SE) from baseline to day 28 in the respiratory domain of the CFQ-R <sup>c,e</sup>	4.66 (1.374)	4.94 (1.118)	No significant difference between nebulised levofloxacin and placebo: LS mean difference 0.28; 95% CI -2.30 to 2.85 <sup>d</sup>
<b>Safety<sup>f</sup></b>	n=219	n=110	
Participants reporting treatment emergent serious adverse events <sup>g</sup>	3.2%	0	No statistical analysis reported
Adverse events leading to withdrawal from study	1.8% (4/219)	0.9% (1/110)	

Treatment emergent adverse events leading to discontinuation of study drug <sup>h</sup>	14.6%	12.7%	
Dysgeusia (taste disturbance)	35.2% (77/219)	0	
Arthralgia	3.2% (7/219)	2.7% (3/110)	

Abbreviations: CFQ-R, [cystic fibrosis questionnaire-revised](#); CFU, colony forming units; CI, [confidence interval](#); FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, [hazard ratio](#); ITT, intention-to-treat; LS, least squares; SD, standard deviation; SE, standard error.

<sup>a</sup> ITT population defined as all randomised participants.

<sup>b</sup> An exacerbation was defined by any of the following: concurrently having changes in at least 4 out of the 12 respiratory signs or symptoms that make up the modified [Fuchs definition](#), independent of an investigator decision to treat with an antibiotic; early discontinuation from the study; death or treatment with an antipseudomonal antibiotic for an event that did not meet the predefined criteria but was determined to be an exacerbation for the purposes of the primary endpoint by an independent, blinded, exacerbation adjudication committee. The 12 respiratory signs and symptoms of the modified Fuchs definition are: change in sputum, new or increased haemoptysis, increased cough, increased dyspnoea, malaise, fatigue or lethargy, temperature above 38<sup>0c</sup>, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in pulmonary function by 10% or more from a previously recorded value and radiographic changes indicative of pulmonary infection.

<sup>c</sup> Information on the outcomes from this study has been supplemented and clarified using the EPAR for [Quinsair](#).

<sup>d</sup> Based on the hierarchical testing procedure used in the study, if the primary endpoint did not show a statistically significant difference, the treatment comparisons for the secondary endpoints were to be considered as exploratory.

<sup>e</sup> The CFQ-R measures health-related quality of life for young people and adults with cystic fibrosis. The respiratory domain of the CFQ-R: consists of multiple questions with generic and disease specific scales. Three versions of the CFQ-R were used in the study based on the age of the participant. The average score of the questions associated with each domain on each version was calculated and converted on a scale from 0 to 100 so the scores were analysed the same way across the versions.

<sup>f</sup> Safety population: all randomised participants who received at least 1 dose of study medication. No statistical analysis was reported for the safety outcomes.

<sup>g</sup> Treatment emergent serious adverse events excluding disease progression.

<sup>h</sup> Treatment emergent adverse events leading to discontinuation of study drug – this included participants who required antibiotics because of worsening respiratory symptoms or exacerbation. The 14.6% in the levofloxacin group included 9.6% due to disease progression and 2.3% due to dysgeusia, the 12.7% in the placebo group included 11.8% due to disease progression.

- Design: multicentre, open label active comparator randomised trial of 3 cycles of treatment with each cycle consisting of 28 days treatment and 28 days follow-up. Conducted in 6 countries: US, Israel, France, Germany, Ireland and the UK, although 68% of participants were from the US. [Allocation was concealed](#). Participants and study co-ordinators were aware of the treatment assignment but the site investigators and medical monitors remained blinded.
- Population: the study included 282 people (57% male) 12 years of age and over (mean age 28 years; 86% were over 18 years of age) with a documented diagnosis of cystic fibrosis, a forced expiratory volume in 1 second (FEV<sub>1</sub>) between 25% and 85% predicted (mean 54%) and a chronic airways infection with *P. aeruginosa* who had received at least three 28 day courses (or a total of 84 days) of inhaled tobramycin over the previous 12 months, with at least a 14 day course completed within the previous 29 to 56 days. Although people who had received antipseudomonal antibiotics in the past 28 days (with the exception of maintenance oral azithromycin) were excluded from the study. Over the previous 12 months, participants had had a mean of 6 courses of inhaled antibiotics. Chronic *P. aeruginosa* infection was defined as a respiratory secretion culture positive for *P. aeruginosa* in the previous 12 months and a positive culture obtained at the screening visit. Participants had not smoked within the previous 28 days and had agreed not to smoke for the duration of the study.
- Intervention and comparison: participants were randomised 2:1 to either levofloxacin 240 mg nebulised twice a day or tobramycin 300 mg nebulised twice daily. Tobramycin was delivered via a PARI LC Plus nebuliser with compressor and levofloxacin was delivered via a PARI investigational eFlow nebuliser. Participants were able to continue their routine respiratory care and medications during the study. Antipseudomonal antibiotics other than the study drug were not allowed unless it was deemed necessary to treat a suspected exacerbation by the study investigator.
- Outcomes: the primary efficacy outcome was the relative change in FEV<sub>1</sub> percent predicted from baseline to day 28. The study was designed to show the non-inferiority of nebulised levofloxacin to nebulised tobramycin



for the primary outcome with a pre-specified non-inferiority margin of a lower 95% confidence interval greater than -4%. If non-inferiority was demonstrated then a subsequent test for superiority of levofloxacin was to be conducted. The primary outcome was conducted for the ITT population (defined as all randomised participants); no results were presented for the per-protocol population. For the primary endpoint and selected secondary endpoints treatment groups were compared using an analysis of variance (ANCOVA) model adjusting for variables including geographic region, age and baseline FEV<sub>1</sub>. Secondary and additional outcomes included time to first exacerbation of cystic fibrosis lung disease, time to administration of antipseudomonal antibiotics other than the study drug, change from baseline in CFQ-R respiratory symptom score and change from baseline in sputum *P. aeruginosa* density. Safety outcomes included adverse event reporting.

**Table 2 Summary of [Elborn et al. 2015](#)**

	<b>Levofloxacin 240 mg nebulised twice a day</b>	<b>Tobramycin 300 mg nebulised twice a day</b>	<b>Analysis</b>
Randomised	n=189	n=93	
<b>Efficacy (ITT population)<sup>a</sup></b>	n=189	n=93	
Primary outcome: LS mean (SD) relative change in FEV <sub>1</sub> percent predicted from baseline to day 28	baseline: 54.8% (17.0) 28 days: 56.0% (18.0)  relative change: 2.3 (9.1)	baseline: 53.2% (15.7) 28 days: 53.3% (16.2)  relative change: 0.4 (11.8)	LS mean treatment difference in relative change 1.86%; 95% CI -0.66 to 4.39; p=0.15  levofloxacin non-inferior to tobramycin but not superior
Selected secondary and additional outcomes:			
Median time to first exacerbation (days) <sup>b</sup>	131	90.5	No statistical significant difference between 2 groups HR 0.78; 95% CI 0.57 to 1.07; p=0.15

Median time to administration of antipseudomonal antibiotics other than the study drug (days)	141	110	HR 0.73; 95% CI 0.53 to 1.01; p=0.04
LS mean change (SE) in <i>P. aeruginosa</i> sputum density (log <sup>10</sup> CFUs per gram)	baseline:7.25 (1.62) change from baseline: to day 28 -0.51 (1.75) to day 168 -0.13 (1.62)	baseline:7.15 (1.69) change from baseline: to day 28 -0.87 (1.76) to day 168 -0.25 (1.76)	No statistically significant difference between 2 groups LS mean difference from baseline to day 28: 0.44; 95% CI -0.01 to 0.88; p=0.05 LS mean difference from baseline to day 168:0.18; 95% CI -0.24 to 0.61; p=0.4 <sup>c</sup>
<b>Safety<sup>d</sup></b>	n=182	n=90	
Participants reporting treatment emergent serious adverse events	22.0%	32.2%	No statistical analysis reported
Adverse events leading to withdrawal from study	3.3% (6/182)	1.1% (1/90)	
Dysgeusia	25.3% (46/182)	0	
Arthralgia	5.5% (10/182)	5.6% (5/90)	

Abbreviations: CFU, colony forming units; CI, [confidence interval](#); FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, [hazard ratio](#); ITT, intention-to-treat; LS, least squares; SD, standard deviation; SE, standard error.

<sup>a</sup> ITT population defined as all randomised participants. For non-inferiority studies, analysis should be conducted for the ITT population and per protocol population and non-inferiority can only be confirmed if analyses in both populations support this. However, this study only provided results for the ITT population. A per protocol population was not defined and no results were presented for it.

<sup>b</sup> An exacerbation was defined by any of the following: concurrently having changes in at least 4 out of the 12 respiratory signs or symptoms that make up the modified [Fuchs definition](#), independent of an investigator decision to treat with an antibiotic; death or treatment with an antipseudomonal antibiotic for an event that did not meet the predefined criteria but was determined to be an exacerbation for the purposes of the primary endpoint by an independent, blinded, exacerbation adjudication committee. The 12 respiratory signs and symptoms of the modified Fuchs definition are: change in sputum, new or increased haemoptysis, increased cough, increased dyspnoea, malaise, fatigue or lethargy, temperature above 38<sup>0c</sup>, anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in pulmonary function by 10% or more from a previously recorded value and radiographic changes indicative of pulmonary infection.

<sup>c</sup> The change from baseline to day 168 for this outcome was an exploratory endpoint.

<sup>d</sup> Safety population: all randomised participants who received at least 1 dose of study medication. Seven participants did not receive nebulised levofloxacin and 3 participants did not receive nebulised tobramycin. No statistical analysis was reported for the safety outcomes.

## Clinical effectiveness

The European Public Assessment Report (EPAR) for [Quinsair](#) commented that the clinical development programme for nebulised levofloxacin occurred during a period of change in the management of chronic *P. aeruginosa* infection in clinical practice. The EPAR states that it is now common practice to rotate inhaled antibiotics by cycle so studies that require administration of repeated cycles of the same product are unlikely to be feasible, also very few participants naive to inhaled antibiotic treatment can be enrolled to studies, in addition the age at which chronic colonisation with *P. aeruginosa* occurs has generally increased which has impacted on the number of young people who can be recruited to studies.

Nebulised levofloxacin has been compared with placebo over 1 cycle of treatment (28 days treatment and 28 days follow-up) in [Flume et al. 2015](#) and compared with nebulised tobramycin over 3 cycles of treatment in [Elborn et al. 2015](#). Both studies included participants aged 12 years and older with a diagnosis of cystic fibrosis and chronic *P. aeruginosa* infection who had

received at least three 28 day courses (or a total of 84 days) of inhaled antibiotics in Flume et al. (2015) or inhaled tobramycin in Elborn et al. (2015) in the previous 12 months and had an FEV<sub>1</sub> between 25% and 85% predicted.

After 28 days treatment, in [Flume et al. 2015](#) there was no statistical significant difference for the primary outcome of time to first exacerbation of cystic fibrosis lung disease compared with placebo. Because of how an exacerbation was defined in the study (see table 1 for details), treatment with an antipseudomonal antibiotic other than the study drug was not classified as an exacerbation unless other criteria were met. In addition, not all events classed as exacerbations were accompanied by initiation of an antipseudomonal antibiotic. However, there was also no statistical significant difference between nebulised levofloxacin and placebo for time to administration of antipseudomonal antibiotics (HR 0.85; 95% CI 0.61 to 1.18).

The [EPAR for Quinsair](#) concluded that it is unclear why Flume et al. (2015) did not show a statistically significant difference for the primary outcome against placebo, although the manufacturers have suggested a number of potential reasons (see [evidence strengths and limitations](#)). For the secondary outcome of change from baseline in [CFQ-R](#) respiratory symptom score (a health-related quality of life measure) there was also no significant difference between nebulised levofloxacin and placebo (see table 1 for details). A treatment difference was found between nebulised levofloxacin and placebo for mean change from baseline to day 28 in FEV<sub>1</sub> percent predicted and *P. aeruginosa* log<sub>10</sub> CFUs per gram sputum density (secondary outcomes, see table 1 for details). However, the clinical significance of these differences (1.31% for mean change in FEV<sub>1</sub> percent predicted and -0.63 for mean change in sputum density) is unclear. In addition, as there was no statistically significant difference between nebulised levofloxacin and placebo for the primary outcome, treatment comparisons for the secondary endpoints should be considered as exploratory only.

In [Elborn et al. 2015](#) nebulised levofloxacin was shown to be non-inferior to nebulised tobramycin for relative change in FEV<sub>1</sub> percent predicted from baseline to day 28 (see table 2 for details). Results were only presented for

the ITT population, however, for non-inferiority studies, analysis should be conducted for both the ITT and per protocol populations (see European Medicines Agency guidance on [Points to consider on switching between superiority and non-inferiority](#) see evidence strengths and limitations for further information). The pre-specified non-inferiority margin of a lower 95% confidence interval greater than -4% had been agreed with the committee for medicinal products for human use ([CHMP](#)) and was the same as that used in the phase 3 study with the same primary outcome comparing nebulised aztreonam with nebulised tobramycin (EPAR: Quinsair).

Participants in Elborn et al. 2015 had received at least 3 courses of inhaled tobramycin in the previous 12 months. The EPAR for Quinsair comments that a comparison of change in FEV<sub>1</sub> between tobramycin and a first cycle of levofloxacin in people naive to levofloxacin but not tobramycin could be biased in favour of levofloxacin. However, it acknowledges that this also applies to other recent license applications for inhaled antibiotics for treating chronic *P. aeruginosa* infection in cystic fibrosis such as nebulised aztreonam. Nebulised levofloxacin was not found to be superior to tobramycin for relative change in FEV<sub>1</sub> percent predicted. The EPAR further comments that this may have allayed concerns regarding the limited value of showing non-inferiority against a treatment that no longer achieves a discernible effect on FEV<sub>1</sub>. A similarly designed study in 273 people aged 6 and over (mean age 26; mean FEV<sub>1</sub> percent predicted 52%) with cystic fibrosis and chronic *P. aeruginosa* infection previously treated with inhaled antibiotics (with 85% of participants having had at least 84 days of inhaled tobramycin over the previous year) showed superiority as well as non-inferiority for nebulised aztreonam compared with nebulised tobramycin for the same FEV<sub>1</sub> primary outcome ([Assael et al. 2013](#)). However, there are no published studies which directly compare nebulised levofloxacin and nebulised aztreonam.

In Elborn et al. (2015) there was no statistically significant difference between nebulised levofloxacin and nebulised tobramycin for median time to first exacerbation or mean change in *P. aeruginosa* sputum density (secondary outcomes: see table 2 for details). The CFQ-R respiratory symptom scores

were similar between the 2 groups at baseline, the score increased (improved) in the levofloxacin group and decreased in the tobramycin group at day 28 (with a difference of 3.19 units [on a scale of 0 to 100];  $p=0.05$ ). However, the results were similar between the 2 groups at the end of the study. The median time to administration of an antipseudomonal antibiotic was 141 days in the levofloxacin group and 110 days in the tobramycin group (HR 0.73; 95% CI 0.53 to 1.01;  $p=0.04$ ). The proportion of people hospitalised for a respiratory exacerbation over the 168 days of the study was lower in the levofloxacin group than the tobramycin group (17.5% compared with 28.0%,  $p$  values provided for nominal significance only and they were not adjusted for multiple variables).

### **Clinical efficacy in children and young people aged 12 to 17 years**

Levofloxacin nebuliser solution is not licensed for use in children and young people aged less than 18 years. The EPAR for Quinsair reports that Flume et al. (2015) included 46 children and young people aged 12 to 17 years and it provides results from a post-hoc analysis for this population for exacerbation-free survival rates at day 56. These were 53.3% (16/30) for nebulised levofloxacin and 25% (4/16) for placebo although the difference was not statistically significant (HR 0.51; 95% CI 0.22 to 1.15;  $p=0.0693$ ). Elborn et al. (2015) only included 28 children and young people aged 12 to 17 years (19 randomised to levofloxacin and 9 to tobramycin). The manufacturers had originally submitted a license application which included children and young people from the age of 12 and 30 kg body weight. However, due to safety concerns (see safety and tolerability section) the manufacturer withdrew the license application for children and young people under 18. The EPAR concluded that currently use cannot be recommended for people aged less than 18 years. Further safety studies including safety studies in children and young people under 18 are planned.

## **Safety and tolerability**

The [EPAR for Quinsair](#) reported that serum concentrations of levofloxacin from nebulised administration were on average approximately 50% of that seen with oral and intravenous routes of administration (at a dose of 500 mg daily). Therefore all of the possible adverse effects associated with oral or intravenous administration of levofloxacin (with the exception of those specific to the route of administration) are also a potential risk with the nebulised formulation. This is reflected in the summary of product characteristics (SPC: [Quinsair](#)) which includes warnings and precautions for use associated with systemic administration of levofloxacin and the fluoroquinolone class of antibiotics, as well as those specific for inhaled administration (such as bronchospasm). The EPAR reports that currently more than 400 people with cystic fibrosis have been exposed to nebulised levofloxacin in clinical studies, most (257) in single cycle studies. However, approximately 14% of participants discontinued the studies early and not all of those who completed the studies received at least 80% of the assigned treatment. The EPAR reports that the observed adverse event profile indicates that levofloxacin nebuliser solution (which contains magnesium chloride) is fairly irritant to the upper and lower airways; however, the discontinuation rates due to these effects were modest. The EPAR further reports that there were relatively few fluoroquinolone class associated adverse events in the studies but that hepatotoxicity and possibly tendon and cartilage disorders and peripheral neuropathy are potential risks of treatment. The EPAR concludes that the long-term safety profile of nebulised levofloxacin in adults remains unclear and that a post-authorisation long-term safety study is planned.

In [Flume et al. 2015](#), 97.7% (204/219) of participants in the nebulised levofloxacin group and 98.2% (108/110) in the placebo group reported at least 1 adverse event. The treatment emergent adverse events reported for at least 5% more participants in the levofloxacin group than the placebo group were dysgeusia (35.2% [77/219] compared with 0), cough (56.6% [124/219] compared with 46.4% [51/110]), pyrexia (7.3% [16/219] compared with 1.8% [2/110]) and nausea (6.4% [14/219] compared with 0.9% [1/110]). The percentage of participants reporting treatment emergent serious adverse

events and treatment emergent adverse events leading to discontinuation of the study drug are reported in table 1. No statistical analysis was presented for the safety outcomes. Regarding fluoroquinolone class adverse effects, the study reported no treatment emergent adverse events related to myasthenia gravis, severe cutaneous adverse reactions, convulsions, peripheral neuropathy, psychosis, ocular toxicity or *Clostridium difficile* associated diarrhoea. The percentage of participants reporting arthralgia was similar between the 2 groups (see table 1). One participant in the levofloxacin group had tendonitis, but there were no reports of tendon rupture. One participant in the levofloxacin group had a prolonged QTc interval, this occurred on study day 53, (25 days after the last dose of study medication). Reports of increased blood glucose or hyperglycaemia were similar between the 2 groups (3.2% of participants in the levofloxacin group and 3.6% in the placebo group), and they were all reported in participants with a history of diabetes. There was 1 report of decreased blood glucose or hypoglycaemia in each group.

In [Elborn et al. 2015](#), 98.9% (180/182) of participants in the nebulised levofloxacin group and 100% (90/90) in the nebulised tobramycin group reported at least 1 adverse event. The treatment emergent adverse events reported for at least 5% more participants in the levofloxacin group than the tobramycin group were dysgeusia (25.3% [46/182] compared with 0%), cough (58.2% [106/182] compared with 53.3% [48/90]), increased sputum (52.2% [95/182] compared with 44.4% [40/90]), paranasal sinus hypersecretion (26.9% [49/182] compared with 20.0% [18/90]) and sinus headache (19.2% [35/182] compared with 14.4% [13/90]). The percentage of participants reporting treatment emergent serious adverse events and adverse events leading to withdrawal from the study are reported in table 2. No statistical analysis was presented for the safety outcomes. The percentage of participants reporting arthralgia was similar between the 2 groups (see table 2). One participant in the levofloxacin group had a serious adverse event of costochondritis (inflammation of cartilage that joins the ribs to the sternum) which led to discontinuation of the study drug. Another participant in the levofloxacin group had symptoms consistent with tendonitis but there were no reports of tendon rupture.



[Elborn et al. 2016](#) was an optional single arm (levofloxacin only) 3 cycle extension study to Elborn et al. (2015). There were 88 participants who enrolled onto the extension study, 56 who continued treatment with nebulised levofloxacin and 32 who changed treatment from nebulised tobramycin to levofloxacin. It was reported that no new onset clinically significant adverse events were seen during the extension study. Treatment emergent adverse events that led to discontinuation of levofloxacin occurred in 4 people (pulmonary exacerbation in 2 people, plantar fasciitis for 1 person and haemoptysis for 1 person).

Levofloxacin nebuliser solution is contra-indicated in people with a history of tendon disorders related to fluoroquinolones, people with epilepsy, pregnant or breast feeding women and people who have a hypersensitivity to levofloxacin or any other fluoroquinolone antibiotic (SPC: [Quinsair](#)). The SPC also states that use is not recommended in people with severe renal impairment (creatinine clearance less than 20 ml/min) and that the safety and efficacy has not been established in people under the age of 18 or aged 65 and over. The SPC reports that the most frequently reported adverse reactions in studies were cough (54%), dysgeusia (30%) and fatigue or asthenia (25%). See the [SPC](#) for further information on contraindications, warnings and precautions for use, potential interactions and adverse effects of nebulised levofloxacin.

### **Safety and tolerability in children and young people aged 12 to 17 years**

Levofloxacin nebuliser solution is not licensed for use in children and young people under 18. The majority of participants in Flume et al. (2015) and Elborn et al. (2015) were over 18 years (85% and 86% respectively). The EPAR reports that the treatment emergent adverse event profile in the small number of children and young people aged 12 to 17 years included in the studies did not appear to be very different to that for adults.

The manufacturers had originally submitted a license application which included children and young people aged from 12 years and 30 kg body weight. The EPAR stated that considering the extent of systemic absorption

from the nebulised route of administration there were major concerns regarding the safety of 28 day cycles in children and young people under 18 that could not be addressed from the available data. In particular, the EPAR highlighted the additional risks of the potential effects on cartilage in people aged under 18 years. The EPAR commented that although fluoroquinolones were already widely used in people with cystic fibrosis under 18, this is usually short term use for treating exacerbations. The EPAR concluded that as other treatments are available for the management of chronic *P. aeruginosa* infection in people under the age of 18, it is not possible to justify the use of nebulised levofloxacin for this age group. On this basis, the manufacturers withdrew the license application for children and young people under 18. As reported in the EPAR, there are a number of safety studies planned which will include children and young people under 18.

### **Evidence strengths and limitations**

Nebulised levofloxacin has been compared with placebo over 1 cycle of treatment and nebulised tobramycin over 3 cycles of treatment in a population of people who have been previously treated with nebulised tobramycin. There are no published studies which directly compare it with nebulised aztreonam. There are also no published studies comparing nebulised levofloxacin with another inhaled antibiotic in a population of people naive to both antibiotics. However, as highlighted in the [EPAR for Quinsair](#) the clinical development programme occurred during a period of change in the management of chronic *P. aeruginosa* infection in clinical practice and it is now common practice to rotate inhaled antibiotics by cycle so very few participants naive to inhaled antibiotic treatment can be enrolled to studies .

The EPAR concluded that it was unclear why in [Flume et al. 2015](#) no statistically significant difference was seen between nebulised levofloxacin and placebo for the primary outcome of time to first exacerbation of cystic fibrosis lung disease. However, the manufacturers did suggest a number of potential reasons. The exacerbation definition used in the study required concurrently having changes in at least 4 out of the 12 respiratory signs or symptoms that make up the modified [Fuchs definition](#), independent of an

investigator decision to treat with an antibiotic. The manufacturers questioned if this was an appropriate exacerbation definition to use and whether time to antibiotic treatment, although subjective would have been a more appropriate measure. However, there was also no statistically significant difference between levofloxacin and placebo for time to administration of antipseudomonal antibiotics other than the study drug. The manufacturers also highlight that there was a baseline imbalance between the 2 groups for number of pulmonary exacerbations in the previous year with 34% of participants in the levofloxacin group having 3 or more exacerbations and 20% in the placebo group have 3 or more. However, the EPAR reported that the hazard ratios for post-hoc analyses for time to exacerbation stratified by number of pulmonary exacerbations favoured placebo for those with more than 5 exacerbations in the last 12 months. The study also only included 1 cycle of treatment which may have been insufficient to assess efficacy.

There were treatment differences between nebulised levofloxacin and placebo for the secondary outcomes on FEV<sub>1</sub> percent predicted and *P. aeruginosa* sputum density. However, the clinical significance of these treatment differences is unclear. In addition, as there was no statistical significant difference between nebulised levofloxacin and placebo for the primary outcome, treatment comparisons for the secondary endpoints should be considered as exploratory only.

In [Elborn et al. 2015](#) nebulised levofloxacin was found to be non-inferior but not superior to nebulised tobramycin for a disease orientated lung function primary outcome. As discussed in the EPAR a comparison between tobramycin and a first cycle of levofloxacin in people naive to levofloxacin but not tobramycin could be biased in favour of levofloxacin. However, it acknowledges that this also applies to other recent license applications for inhaled antibiotics for treating chronic *P. aeruginosa* infection in cystic fibrosis such as nebulised aztreonam.

For non-inferiority studies, analysis should be conducted for the ITT population and per protocol population; non-inferiority can only be confirmed if both populations support this. The European Medicines Agency guidance on

[Points to consider on switching between superiority and non-inferiority](#) states that in a non-inferiority trial, the full analysis set (ITT population) and the per protocol analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation of the study results. However, Elborn et al. (2015) did not define a per protocol population and results were only provided for the ITT population. Elborn et al. (2015) was an open-label study which could lead to bias, Flume et al. (2015) was blinded, although it was not blinded for taste.

There is a lack of long-term safety and efficacy data. As reported in the EPAR less than 150 participants received 3 cycles of treatment and less than 50 participants received 6 cycles of treatment.

The majority of participants in the 2 studies were over 18 years and the mean ages were 28 and 29. As stated in the SPC, the safety and efficacy of levofloxacin nebuliser solution has not been established in people under the age of 18 or aged 65 and over. People with severe renal impairment (creatinine clearance less than 20 ml/min) were excluded from the studies.

## **Context**

### **Alternative treatment**

Inhaled antibiotic treatments currently licensed in the UK for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in people with cystic fibrosis include: colistimethate sodium, a polymyxin antibiotic ([Promixin powder for nebuliser solution](#), [colomycin powder for solution for injection, infusion or inhalation](#) and [Colobreathe](#) a dry powder for inhalation); tobramycin, an aminoglycoside antibiotic ([Bramitob nebuliser solution](#), [Tobi nebuliser solution](#) and [Tobi podhaler](#) a dry powder for inhalation); aztreonam, a beta-lactam antibiotic ([Cayston powder and solvent for nebuliser solution](#)); and levofloxacin, a fluoroquinolone antibiotic ([Quinsair](#) nebuliser solution). Levofloxacin nebuliser solution is not licensed for use in children and young people under 18. The other available inhaled preparations are licensed for use

in children, however the age from which they are licensed varies between the individual products; please see the individual SPCs for further information.

### Costs of alternative treatment

Drug	Dose	Estimated cost for 28 days treatment (excluding VAT)
levofloxacin nebuliser solution ( <a href="#">Quinsair</a> ) <sup>a</sup>	240 mg (1 ampoule) nebulised twice a day	£2181.53 <sup>g</sup>
nebulised aztreonam ( <a href="#">Cayston powder and solvent for nebuliser solution</a> ) <sup>b</sup>	75 mg (1 vial) nebulised three times in 24 hours	£2181.53 <sup>g</sup>
nebulised colistimethate sodium ( <a href="#">Promixin powder for nebuliser solution</a> ) <sup>c</sup>	1 million international units (1 vial) nebulised twice a day <sup>c</sup>	£313.60 <sup>g</sup>
nebulised colistimethate sodium (using <a href="#">Colomycin powder for solution for injection, infusion or inhalation</a> ) <sup>c</sup>	1 to 2 million international units nebulised twice a day <sup>c</sup>	£100.80 to £181.44 <sup>g</sup>
colistimethate dry powder for inhalation ( <a href="#">Colobreathe</a> ) <sup>d</sup>	125 mg (1 capsule) inhaled twice a day	£968.80 <sup>g</sup>
nebulised tobramycin ( <a href="#">Bramitob nebuliser solution</a> ) <sup>e</sup>	300 mg (1 single-dose container) nebulised twice a day	£1187.00 <sup>g</sup>
nebulised tobramycin ( <a href="#">Tobi nebuliser solution</a> ) <sup>e</sup>	300 mg (1 ampoule) nebulised twice a day	£1305.92 <sup>h</sup>
tobramycin dry powder for inhalation ( <a href="#">Tobi podhaler</a> ) <sup>f</sup>	112 mg (4 capsules) inhaled twice a day	£1790.00 <sup>g</sup>

Doses shown are example doses and do not imply therapeutic equivalence. For prescribing information please refer to the relevant [summary of product characteristics](#).

<sup>a</sup> [Quinsair](#) is licensed for use in adults aged 18 years and older.

<sup>b</sup> [Cayston powder and solvent for nebuliser solution](#) is licensed for use in adults and children aged 6 years and older.

<sup>c</sup> [Promixin powder for nebuliser solution](#) and [colomycin powder for solution for injection, infusion or inhalation](#) are licensed for use in adults and children. The dose ranges presented here are example doses for adults and do not represent the full licensed dose range.

<sup>d</sup> [Colobreathe](#) is licensed for use in adults and children aged 6 years and older.

<sup>e</sup> [Bramitob nebuliser solution](#) and [Tobi nebuliser solution](#) are both licensed for use in adults and children aged 6 years and older.

<sup>f</sup> [Tobi podhaler](#) is licensed for use in adults and children aged 6 years and older.

<sup>g</sup> Prices based on [MIMS](#) June 2016

<sup>h</sup> Prices based on [Drug Tariff](#) June 2016

Costs provided are the drug costs presented in MIMS and the Drug Tariff. They do not include any additional costs that may be associated with nebulisation such as equipment or staffing costs and do not take patient access schemes into consideration.

## ***Estimated impact for the NHS***

### **Likely place in therapy**

Levofloxacin nebuliser solution is the first nebulised fluoroquinolone antibiotic to be licensed for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis. Other licensed inhaled treatments include: colistimethate sodium (a polymyxin antibiotic), tobramycin (an aminoglycoside antibiotic) and aztreonam (a beta-lactam antibiotic).

The [NHS England clinical commissioning policy on inhaled therapy for adults and children with cystic fibrosis](#) (published January 2015) details the clinical criteria under which NHS England will routinely fund inhaled therapies (including colistimethate sodium, tobramycin and aztreonam) for people with cystic fibrosis. The policy recommends a stepwise approach to treatment for chronic *P. aeruginosa* infection. Colistimethate sodium is recommended first-line when pulmonary function is normal but chronic *P. aeruginosa* infection is evident. Tobramycin is recommended second-line if despite continued therapy and good adherence to treatment; lung function continues to decline or there

is a requirement for more than 1 course of intravenous antibiotics in the preceding year. This may be prescribed in an alternative monthly regimen rotated with colistimethate sodium. Aztreonam is recommended third-line if there is further decline in lung function or exacerbations requiring intravenous antibiotics as further described and specified in the policy. Aztreonam may be prescribed in an alternative monthly regimen rotated with either colistimethate sodium or tobramycin depending on the clinical response to those medications previously.

The aim of treatment with inhaled antibiotics in chronic lung infection in people with cystic fibrosis is to reduce the bacterial load in the lung, which in turn should reduce inflammation in the lung, thereby reducing lung damage and so reducing the rate of deterioration of lung function and frequency of exacerbations of infection ([Ryan et al. 2011](#)). Nebulised levofloxacin was shown to be non-inferior but not superior to nebulised tobramycin for relative change in FEV<sub>1</sub> percent predicted in a population of people with a diagnosis of cystic fibrosis and chronic *P. aeruginosa* infection who had received at least three 28 days courses of inhaled tobramycin in the previous 12 months. No statistically significant difference was found between nebulised levofloxacin and placebo for time to first exacerbation of cystic fibrosis lung disease although a treatment difference was found for FEV<sub>1</sub> percent predicted and *P. aeruginosa* sputum density, however, the clinical significance of these differences is unclear.

The [EPAR for Quinsair](#) concluded that the addition of nebulised levofloxacin to the 3 inhaled antibiotics already licensed for this indication would allow for further rotational cyclical regimens of treatments from different classes. Due to the extent of systemic absorption of levofloxacin after inhalation, the adverse effects associated with systemic administration of levofloxacin are also a risk with the nebulised route of administration. The EPAR added that there is a need to further characterise the safety profile that will be associated with chronic substantive systemic exposure in adults and long-term safety studies are planned.

Levofloxacin nebuliser solution is only licensed for use in adults aged 18 years and over. The other available inhaled antibiotic preparations are licensed for use in children; however the age from which they are licensed varies between the individual products (see the cost of alternative treatment table for details of other licensed preparations). The EPAR for Quinsair concluded that currently use cannot be recommended for people aged less than 18 years due to safety concerns such as the lack of long-term data, predicted serum concentrations after inhalation and the additional potential risk of adverse effects on cartilage in adolescents (see safety and tolerability section).

Levofloxacin nebuliser solution is nebulised over 5 minutes twice a day; by comparison aztreonam is nebulised over 2 to 3 minutes 3 times a day.

The cost of 28 days treatment with nebulised levofloxacin is the same as the cost of 28 days treatment with nebulised aztreonam. However it is more expensive than colistimethate sodium and tobramycin, in either the nebulised or dry powder inhalation formulations (see the cost of alternative treatment table for further details).

### **Estimated usage**

Based on data from the UK cystic fibrosis registry report the manufacturers estimate that 48% of people with cystic fibrosis have chronic *P. aeruginosa* infection (defined as 3 or more infections per year). The manufacturers suggest that the potential place in therapy for nebulised levofloxacin would be a third-line treatment option for people who have been previously treated with inhaled tobramycin. The manufacturers anticipate that nebulised levofloxacin will acquire an increasing proportion of the market share of nebulised aztreonam prescribing.

### ***Relevance to NICE guidance programmes***

Levofloxacin nebuliser solution was not considered appropriate for a NICE technology appraisal. NICE has issued technology appraisal guidance on [colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis](#) and [mannitol dry powder for inhalation for treating cystic fibrosis](#). A [NICE technology appraisal on](#)



[lumacaftor - ivacaftor for treating cystic fibrosis homozygous for the F508del mutation](#) has also been published.

A NICE guideline on [diagnosis and management of cystic fibrosis](#) is in development. The expected date of publication is October 2017. The [final scope](#) includes antimicrobial management in cystic fibrosis to treat chronic pulmonary infection, including clinical exacerbations and colonisation as a key area that will be covered in the guideline.

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### ***Development of this evidence summary***

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

### **Expert advisers**

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### **Declarations of interest**

Dr Rowland Bright-Thomas: No interests declared

Dr Simon Doe: Received single payment from Novartis for advisory work on an online education tool being developed for asthma (2016)

### **About this evidence summary**

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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