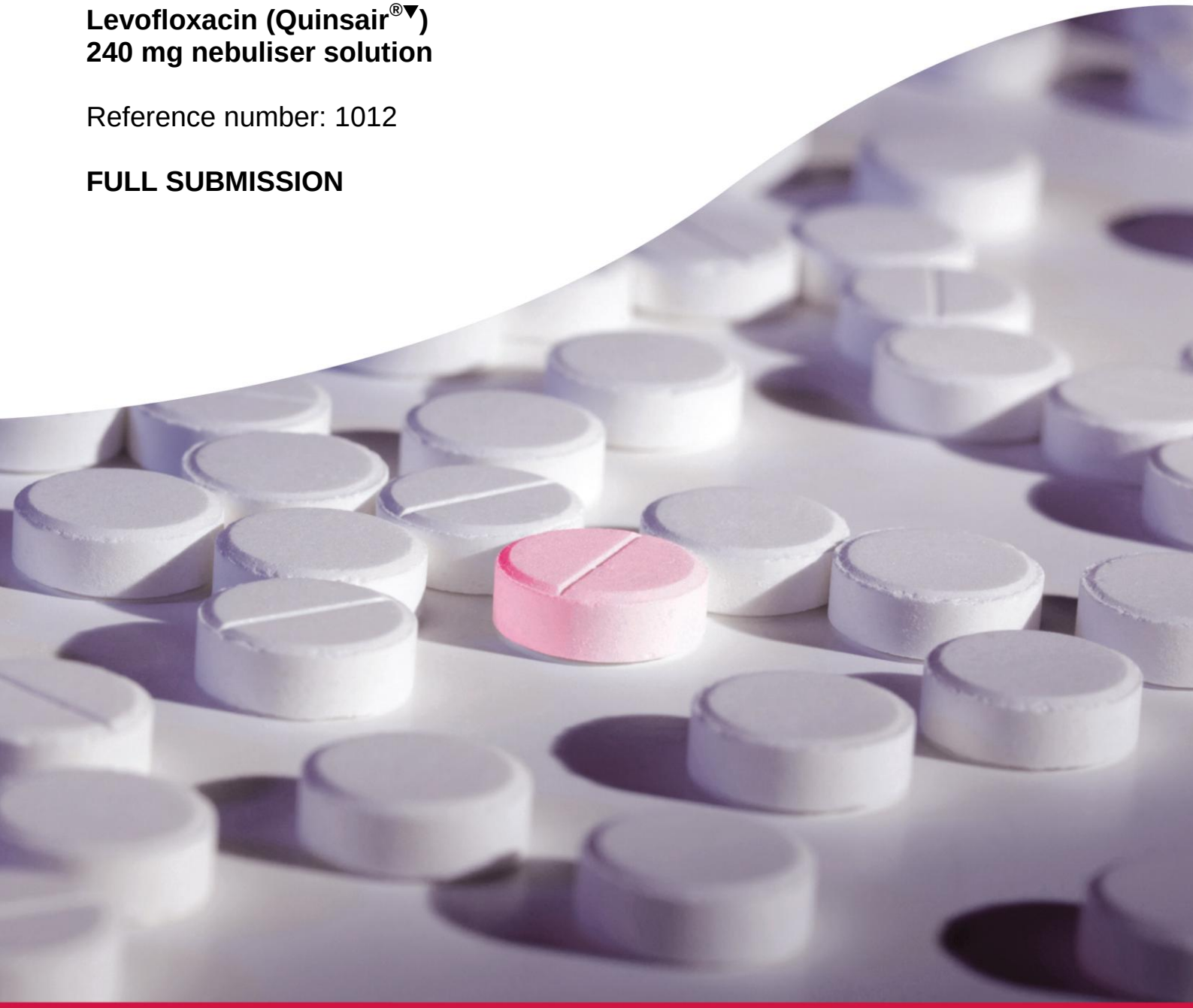
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Levofloxacin (Quinsair®▼) 240 mg nebuliser solution

Reference number: 1012

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Levofloxacin (Quinsair®▼) 240 mg nebuliser solution

This assessment report is based on evidence submitted by Raptor Pharmaceuticals Europe B.V.[1]

1.0 PRODUCT DETAILS

Licensed indication under consideration	Levofloxacin (Quinsair®▼) 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[2].
Dosing	Recommended dosage is 240 mg (one ampoule) administered by inhalation twice daily, as close as possible to 12 hours apart. Dosage is taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. Cyclical therapy may be continued as long as the physician considers that the patient is obtaining clinical benefit. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	26 March 2015[3]

2.0 DECISION CONTEXT

2.1 Background

Cystic fibrosis (CF) is the most common recessively inherited disease in the UK, resulting from mutations affecting a gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel that regulates salt and water transport across the cell membrane[4]. This leads to thickened secretions across the epithelial cell lining of various organs, including the lungs where the clearance of microorganisms becomes impaired[4]. Therefore, patients with CF suffer from chronic infections of the lower respiratory tract, the most common being *Pseudomonas aeruginosa* infection[5,6]. Chronic pulmonary infection with *P. aeruginosa* in CF patients is difficult to eradicate and is implicated as the major source of lung function decline with associated morbidity and mortality[5,7].

CF is a life-limiting, chronically debilitating disease that greatly affects quality of life and significantly reduces survival[5]: the current UK median predicted survival is 40.1 years[8]. In 2014, there were 10,583 CF patients registered in UK, with 216 active patients in Wales[8]. It is reported that 60% of CF patients aged 18–24 years are infected with *P. aeruginosa* and by the age of 25–34 years approximately 80% of patients are infected[5].

The Cystic Fibrosis Trust guidance on antibiotic treatment in cystic fibrosis (2009) recommends regular nebulised antipseudomonal antibiotic treatment for patients with chronic *P. aeruginosa* infection[7]. The guidance recommends initial treatment with nebulised colistimethate sodium; if colistimethate sodium is not tolerated or clinical

progress is unsatisfactory, tobramycin should be used[7,9]. Should a further option be required, aztreonam lysine is recommended for third-line use[9].

Levofloxacin is a broad-spectrum fluoroquinolone with potent bactericidal activity[5]. Levofloxacin nebuliser solution is a new inhaled formulation of levofloxacin intended to be the first inhaled form of fluoroquinolone for use in chronic maintenance therapy in CF[5].

The applicant company has requested that the All Wales Medicine Strategy Group (AWMSG) consider levofloxacin for use in a subgroup of patients within its licensed indication. The proposed subgroup is patients who do not respond to, or are intolerant of, second-line treatment with tobramycin[1]. Therefore, the company ask that levofloxacin be considered as a third-line therapy for the stated indication.

2.2 Comparators

The comparator included in the company submission was aztreonam lysine (Cayston®)[1].

2.3 Guidance and related advice

- Welsh Health Specialised Services Committee (WHSSC). Specialised services clinical access policy: inhaled therapy for patients 6 years and older with cystic fibrosis (2014)[9].
- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK (2011)[4].
- Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis (2009)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation with restrictions for the use of aztreonam lysine (Cayston®)[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from a phase III study (MPEX-209) designed to compare the efficacy and safety of levofloxacin inhalation solution (LIS) with tobramycin inhalation solution (TIS)[1]. Participants of the MPEX-209 study were given the choice to participate in a single-arm extension to evaluate the long term efficacy and safety of LIS treatment (MPEX-209 Extension). Two placebo-controlled studies were also included in the submission (MPEX-204 and MPEX-207); however, these did not compare LIS with an active comparator and are therefore not discussed further[1].

The MPEX-209 and MPEX-209 extension included patients ≥ 12 years of age; however, the licensed indication is for adult patients[1]. The company has provided post-hoc analyses of patients ≥ 18 years of age to reflect the licensed indication and the figures reported in this section refer to the post-hoc subgroup only, unless stated otherwise[1].

In the absence of direct comparative evidence with the comparator aztreonam lysine, the company included a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of LIS, colistimethate sodium, tobramycin and aztreonam lysine for the management of chronic *P. aeruginosa* infections in CF at four weeks and 24 weeks[1].

3.1 MPEX-209

The MPEX-209 trial was a randomised, multicentre, open-label, active-controlled phase III non-inferiority study that compared the efficacy and safety of LIS versus TIS in CF patients with *P. aeruginosa* infection[11]. Patients included in the study were: ≥ 12 years of age with documented CF diagnosis, with a predicted forced expiratory volume in one

second (FEV_1) between 25–85%, had chronic airway infection with *P. aeruginosa*, and had received at least three 28-day courses of inhaled TIS over the 12 months prior to screening[11]. Patients were excluded if an investigational agent was used 28 days prior to first visit or if nebulised or systemic antimicrobials active against *P. aeruginosa* were used up to 28 days prior to first visit.

Patients (n = 254 for ≥ 18 years of age[1]) were randomised 2:1 to receive either 240 mg LIS twice daily or 300 mg TIS twice daily[11]. Three treatment cycles were administered, with each cycle consisting of 28 days on therapy followed by 28 days off therapy[11]. Participants were not permitted to use other antipseudomonal antibiotics other than the study medicine unless deemed necessary by the investigator to treat a suspected exacerbation[11].

The primary outcome of the study was the relative change in FEV_1% predicted from baseline to day 28 (least squares [LS] mean difference)[11]. For the sub-group of participants ≥ 18 years of age, the LS mean relative changes in FEV_1% predicted at day 28 was 2.31% in the LIS-treated group (n = 170) and 0.35% in the TIS-treated group (n = 84)[1]. To determine non-inferiority, a two-sided 95% confidence interval (CI) for the difference between relative change in FEV_1% between LIS and TIS in the intention to treat (ITT) population was calculated[11]. If the lower limit of the 95% CI was above the pre-specified margin of −4%, non-inferiority was claimed[11]. The LS mean difference between the LIS and TIS treatment arms was 1.96 (95% CI −0.65–4.56)[1]. Non-inferiority was met in the post-hoc ITT population for the primary endpoint; the secondary endpoints also demonstrated non-inferiority (see Table 1)[1].

Table 1. Primary and secondary endpoints of the MPEX-209 trial in participants ≥ 18 years of age[1]

Endpoints	LIS (n = 170)	TIS (n = 84)	LIS-TIS Treatment difference (95% CI) p-value
Primary Endpoint			
Relative change in FEV_1% predicted from baseline to day 28, LS mean (SE)[2]	2.31 (0.79)	0.35 (1.11)	1.96 (−0.65–4.56) p = 0.139
Secondary Endpoints			
Absolute change in FEV_1% predicted from baseline to day 28, LS mean (SE)[2]	1.14 (0.38)	−0.10 (0.54)	1.04 (−0.23–2.30) p = 0.11
Time to exacerbation from baseline to final visit, median days (95% CI)	131 (87–154)	77 (48–109)	n/a (n/a) p = 0.0474
LIS: levofloxacin inhalation solution; TIS: tobramycin inhaled solution; CI: confidence interval; FEV: forced expiratory volume; LS: least squares; SE: standard error.			

3.2 MPEX-209 extension

The MPEX-209 extension was a single-arm, optional, non-randomised, open-label extension of the MPEX-209 study to evaluate the long-term efficacy and safety of three additional 56 day cycles of LIS treatment[12]. A total of 76 patients ≥ 18 years of age were enrolled[1]; 46 patients continued LIS treatment (LIS/LIS patients) and 30 patients were switched to LIS after three initial cycles of TIS (LIS/TIS patients)[1].

LIS/LIS participants maintained an improved relative FEV_1% predicted from the core baseline (from 0.09% to 6.10%) throughout the extension study[1]. TIS/LIS participants demonstrated an even greater improvement during the extended treatment period than the LIS/LIS patients, with relative FEV_1% predicted ranging from 3.19–6.64% from core

baseline[1]. The results of the MPEX-209 extension study were consistent with the MPEX-209 study[1].

3.3 Systematic review and NMA

The systematic review included randomised active- or placebo-controlled trials that included adult and children CF patients (≥ six years of age) with chronic *P. aeruginosa* infection[1]. Interventions included the following inhaled antibiotics, at any dose, using any method of delivery: tobramycin, colistimethate sodium, aztreonam lysine, LIS. Outcomes included relative change in FEV_1%, absolute change in FEV_1%, change in *P. aeruginosa* density, hospitalisation[1].

3.3.1 Four Week NMA

A total of nine randomised controlled trials (RCTs; 12 articles) were identified for the four week NMA[1]. Of these RCTs, five included either LIS or the comparator of interest (aztreonam lysine): three trials included LIS directly. Outcome estimates for mean change from baseline to four weeks versus LIS are shown in Table 2.

Table 2. Outcome estimates from the mean change from baseline to four weeks (four week NMA)[1]

	TIS versus LIS	AZT versus LIS	Placebo versus LIS
Relative change in FEV_1% predicted (7 RCTs*), mean change (95% CrI)	−1.870 (−9.476, 5.762)	5.921 (−4.796, 16.610)	−5.283 (−11.550, 0.130)
Absolute change in FEV_1% predicted (5 RCTs*), mean change (95% CrI)	−1.039 (−7.387, 5.291)	2.241 (−6.936, 11.440)	−2.680 (−7.487, 1.756)
P. aeruginosa density change (7 RCTs*), mean change (95% CrI)	−0.150 (−0.659, 0.358)	−0.095 (−0.622, 0.433)	0.643 (0.309, 0.977)
Hospitalisation (1 RCT), RR (95%CrI) †	-	0.955 (−0.051-18.057)	

*RCT numbers quoted refer to all trials included in the network, not all of which included LIS
†Due to insufficient trial numbers, hospitalisation was subjected to an indirect comparison in lieu of an NMA
TIS: tobramycin inhaled solution; LIS: levofloxacin inhalation solution;AZT: aztreonam lysine (75 mg, three times daily); FEV: forced expiratory volume; RCT: randomised control trials; RR: relative risk; CrI: credible interval.

3.3.2 24 Week NMA

A total of seven RCTs (nine articles) were identified for the 24 Week NMA[1]. Of these RCTs, two included either LIS or the comparator of interest (aztreonam lysine): one trial included LIS directly. Outcome estimates for mean change from baseline to 24 weeks versus LIS are shown in Table 3.

Table 3. Outcome estimates from the mean change from baseline to 24 weeks (24 Week NMA)[1]

	TIS versus LIS	AZT versus LIS	Placebo versus LIS
Relative change in FEV_1% predicted (4 RCTs*), mean change (95% CrI)	−0.553 (−3.906, 2.799)	−2.356 (−7.321, 2.626)	−9.660 (−15.010, −4.330)
Absolute change in FEV_1% predicted (4 RCTs*), mean change (95% CrI)	0.278 (−1.361, 1.917)	−0.653 (−3.117, 1.819)	−6.431 (−8.842, −4.022)
P. aeruginosa density change (3 RCTs*), mean change (95% CrI)	−0.180 (−0.688, 0.329)	-	0.221 (−0.36, 0.802)
Hospitalisation (4 RCTs*), OR (95% CrI)	1.920 (1.012, 3.304)	-	3.158 (1.531, 5.784)

*RCT numbers quoted refer to all trials included in the network, not all of which included LIS
TIS: tobramycin inhaled solution; LIS: levofloxacin inhalation solution; AZT: aztreonam lysine (75 mg, three times daily); FEV: forced expiratory volume; RCT: randomised control trials; CrI: credible interval; OR: odds ratio

3.4 Comparative Safety

The company included safety data from the MPEX-209 trial for the subpopulation of patients ≥ 18 years of age (n= 235; 157 patients treated with LIS, 78 patients treated with TIS)[1]. Treatment-emergent adverse events (TEAEs) were reported in 44.6% of LIS patients and 16.7% of TIS patients. The most common TEAEs that were reported by at least 5% more patients in the LIS arm than the TIS arm were cough (55.4% for LIS; 50% for TIS), increased sputum (50.3% for LIS; 42.3% for TIS), paranasal sinus hypersecretion (25.5% for LIS; 17.9% for TIS), fatigue (33.8% for LIS; 28.2% for TIS) and dysgeusia (24.8% for LIS; 0% for TIS). TEAE were reported in 8.9% (14/157) of the LIS treatment arm and 7.7% (6/78) of the TIS treatment arm leading to permanent discontinuation of the study medicine, the most common being disease progression. The safety findings in the MPEX-209 extension study were consistent with the MPEX-209 study[1].

In the NMA, tobramycin and aztreonam lysine were associated with a lower study withdrawal rate for any adverse events; however, the differences were not significant[1].

The Committee for Medicinal Products (CHMP) reported that the long-term safety profile in adults remained unclear and a post-authorisation safety study will investigate the long term safety profile of LIS in normal clinical practice[5].

3.5 AWTTC critique

- The applicant company has requested that LIS be considered for use in a subgroup of patients within its licensed indication who do not respond to, or are intolerant of, tobramycin. The use of LIS after tobramycin reflects clinical guideline recommendations; however, the population of patients in the study does not reflect the third-line use of LIS suggested by the company. Furthermore, the company has suggested that LIS will displace third-line use of aztreonam lysine[1]. However, there is no direct clinical or comparative safety data for LIS versus aztreonam lysine.
- LIS was non-inferior to TIS in relative change from baseline to four weeks in FEV_1%. The NMA reported aztreonam lysine was likely to have a better effect for relative change from baseline to four weeks in FEV_1% than LIS, although the difference was not significant[1]. The results of the NMA should be treated with caution based on heterogeneity of patient characteristics and trial design.
- Antibiotics for chronic *P. aeruginosa* infections in CF patients are limited and there is an unmet need for additional antimicrobial options for this indication.

The availability of LIS may provide a further option for cycling of inhaled antibiotic treatment to limit the risk of treatment resistance and prolong efficacy.
- Aztreonam lysine is administered three times a day whereas LIS is administered twice a day, which may be more convenient for patients[2,13].
- CHMP outlined the need for post-authorisation long-term safety analyses to address concerns of long-term exposure to LIS.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) of LIS (240 mg twice daily) compared to aztreonam lysine nebuliser solution (75 mg three times daily) for the management of chronic pulmonary infections due to *P. aeruginosa* in adult patients with CF who have been previously treated with inhaled tobramycin[1]. Both maintenance treatments are taken in repeated cycles of 28 days on therapy followed by 28 days off therapy.

A Markov model with an NHS perspective developed for the National Institute for Health and Care Excellence (NICE) appraisal of colistimethate sodium dry powder for inhalation (DPI) and tobramycin DPI[14] is used to assess the cost-effectiveness of LIS compared to aztreonam lysine. Patients enter the model when they start treatment at an average age of 28 years in one of three levels of severity of FEV_1 predicted ($FEV_1 \geq 70\%$, FEV_1 40–69% and $FEV_1 < 40\%$). After a treatment cycle, patients can stay at the same FEV_1 level, improve (and transition to lower severity) or worsen. Patients in the $FEV_1 < 40\%$ state can undergo lung transplantation and move to the transplantation state before entering the "post-transplant state". At any point, patients can die from CF-related and other causes. The mortality risk depends on patient age and increased mortality is assumed for patients undergoing lung transplantation. Minor and major exacerbations can be experienced in any health state and are assumed to depend on FEV_1 status and treatment arm. The model adopts a lifetime horizon to accommodate the entire patient pathway and 3.5% discounting is applied to both costs and benefits.

For LIS, all clinical outcome data were derived from the pivotal MPEX-209 trial. In the absence of direct comparative data, the company conducted an NMA with TIS as a reference to estimate exacerbation rates (based on odds ratios [OR] compared to MPEX-209 results) for aztreonam lysine and a subsequent calibration model in a Bayesian framework to estimate transition probabilities between health states for both treatments. Probability of lung transplantation[14], CF related mortality[15] and transplantation mortality[16] were taken from published literature. Cost of aztreonam lysine was derived from the British National Formulary (BNF)[17] and assumed to be equal for LIS. Overall CF cost (including patient care, outpatient attendances, home care support, home visits by the multidisciplinary team, general support for patients and carers, intravenous antibiotics and annual review investigations), cost of transplantation and post-transplant care[16] and cost of exacerbations[14] were taken from published sources and inflated to 2015 prices. Utility values for the different FEV_1 health states[18] and decrements for exacerbations[19] were taken from observational studies and utilities for lung transplant and post-transplant states from a cross-sectional study of patients undergoing lung and heart transplants[20].

Extensive deterministic and probabilistic sensitivity analyses (PSA) are undertaken to assess parameter uncertainty. Scenario analyses are used to explore the effect of shorter time horizons (three and five years), Wales Patient Access Scheme (WPAS) discounted prices, alternative data sources and extrapolation techniques on the results.

4.1.2 Results

The company presents two base case analyses using different discount rates for the LIS price. [Commercial in confidence information removed.] The results of the chosen base case analysis (lifetime horizon, [commercial in confidence information removed]) are presented in Table 4. LIS is found to be [commercial in confidence information removed] less expensive and results in 0.698 more quality-adjusted life-years (QALYs) compared to aztreonam lysine on average per patient over a lifetime horizon and is thus reported to be the dominant treatment option.

Table 4. Results of the base case analysis (lifetime horizon, [commercial in confidence information removed])

Table 5 summarises the scenarios provided by the company in order to address uncertainty around the key input parameters. [Commercial in confidence information removed.] The ICER of the lifetime horizon (no discount applied) is £9,219 when alternative health state baseline utilities are used and is £15,390 when transition probabilities for both treatments are assumed to be equal after 5 years. [Commercial in confidence information removed.]

Table 5. Results of the scenario analyses

Scenarios	ICER	Plausibility
Scenario 1: Alternative source for utilities[14] for FEV_1 ≥ 70% predicted, FEV_1 40–69% predicted, FEV_1 < 40% predicted health states	LIS dominates over 3 and 5 years and ICER of £9,219 over lifetime horizon (no discount) [CIC information removed]	This scenario is plausible. The utility values used in this scenario have been used for health technology assessment before.
Scenario 2: Alternative extrapolation approach (FEV_1 % transition probabilities for LIS set equal to AZT after 5 years).	LIS dominates over 3 and 5 years and ICER of £15,390 over lifetime horizon (no discount) [CIC information removed]	It is uncertain how plausible this scenario is due to the lack of direct comparative evidence and follow-up data that is restricted to 24 weeks.
Scenario 3: Time horizon 3 and 5 years, respectively	LIS cost saving (£117 and £128 per patient) and dominates (no discount)	This scenario is implausible. Considering that CF is a lifelong condition and the model calculates that after 10 years only 18% of patients are in the "dead" health state, short time horizons appear implausible and will favour LIS.
Scenario 4: All sub-scenarios assume CIC discount for LIS a) 0% discount on AZT b) 10% discount on AZT c) 15% discount on AZT d) 20% discount on AZT e) 30% discount on AZT f) 40% discount on AZT g) 50% discount on AZT	[CIC information removed]	The plausibility of these scenarios depends on the WPAS discount agreed for aztreonam lysine.

ICER: incremental cost effectiveness ratio; FEV: forced expiratory volume; LIS: levofloxacin inhalation solution; WPAS: Wales Patient Access Scheme; AZT: aztreonam lysine; CF: cystic fibrosis.
CIC: Commercial in confidence

The results of the deterministic sensitivity analyses indicate that the ICER is sensitive to the cost of LIS, CF costs, discount rate, OR for exacerbations under aztreonam lysine, as well as transplantation probability and mortality parameters when no WPAS discount is applied. [Commercial in confidence information removed.]

4.1.3 AWTTC critique

[Commercial in confidence information removed.]

Strengths of the economic analysis:

- Aztreonam lysine appears to be the appropriate comparator in third-line treatment of chronic *P. aeruginosa* in adults with CF.
- The model used to calculate cost-effectiveness was developed as part of the health technology assessment of colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic *P. aeruginosa* lung infection in CF and as such has been independently reviewed and validated and is very specific to the condition in question.
- The company provides a very detailed and transparent account of all methods and results.
- The methodology used in the systematic literature review, NMA, Bayesian model and cost-effectiveness model is described in detail and appears robust and valid.
- The company uses extensive sensitivity analyses to assess the effect of parameter uncertainty on the results.

Limitations of the economic analysis:

- The comparison to aztreonam lysine restricts the submission for use as a third-line option only.
- Since no data in the adult subpopulation was available for aztreonam lysine, the analysis presented by the company was performed in the full study population of the MPEX-209 trial. This includes 13.8% of participants between 12 and 18 years. Furthermore, the NMA included studies with patients six years and over. It is uncertain to what degree this could introduce bias.
- The MPEX-209 study used to inform the model was an open-label study which could introduce bias.
- The NMA uses tobramycin nebuliser solution as reference but also includes tobramycin powder and colistimethate sodium which could increase study heterogeneity and introduce bias.
- The MPEX-209 study used to inform the health economic analysis was conducted at 95 sites in the US (67.7% of participants) and 28 sites in Germany, France, Ireland, Israel and the UK (four sites, including Llandough). It is unknown how many patients were recruited in the UK and it is therefore unclear how generalisable the results of the study are to the UK (and specifically the Welsh population of CF patients).
- The model assumes that patients do not switch treatment throughout the lifetime horizon. Considering that 12.7% of participants in the LIS group in the pivotal MPEX-209 trial permanently discontinued treatment and the severity of the disease and continued need for treatment, this assumption appears unrealistic and will introduce bias.
- The model assumes that all patients are 100% compliant to therapy. Considering that in the MPEX-209 trial 68.5% of participants were at least 80% adherent, this assumption may overestimate the treatment effect of both comparators.
- The model appears to assume sustained efficacy of LIS and aztreonam lysine over a patient's lifetime. While the MPEX-209 extension study provides

outcome data for up to one year follow-up, there is no longer term data to support this assumption.

- No direct comparative data is available for the comparison of LIS and aztreonam lysine. While the systematic review and NMA conducted by the company appear robust, bias cannot be excluded. This is especially important as clinical outcomes for aztreonam lysine (transition probabilities and exacerbation rates) are assumed worse compared to LIS and the analysis is sensitive to these inputs.
- The utility values used for the FEV_1 health states were derived from a mapping exercise and lung transplant utilities were taken from a study not specific to CF patients which could introduce bias.
- The ICERs vary considerably according to the discount values for the comparator. [Commercial in confidence information removed.]

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-utility of LIS for the maintenance treatment of chronic *P. aeruginosa* in adults with CF.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The most recent CF population statistics[8] from 2014 are used to estimate the number of adults suffering from CF in Wales at 2016. The analysis assumes that a further two patients will reach adulthood every year resulting in a population of 225 by year five based on CF registry data[8]. A mortality rate of 0% is applied as the net patient number is already captured in the adult data. Considering that 48.2% of this adult CF patient population suffers from chronic *P. aeruginosa* infection[8], this results in 104 patients being treated for this condition in year one increasing to 108 in year five. 14.5% of these patients are currently treated with aztreonam lysine giving an eligible population of 15 patients in year one and 24 in year five (assuming 2% growth). The company estimates that LIS will take 20% market share from aztreonam lysine in year one increasing to 80% in year five which would calculate to three patients in year one to 19 patients in year five.

No sensitivity analyses are provided by the company.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 6.

Table 6. Company-reported costs associated with use of LIS

	2017	2018	2019	2020	2021
Number of eligible patients (Patients with *P. aeruginosa* infection)	104	105	106	107	108
Subpopulation of eligible patient cohort (%)	14.5%	16.5%	18.5%	20.5%	22.5%
Number of patients with the condition receiving 3rd line treatment	15	17	19	21	24
Current medicine expenditure with the displaced medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Proportion of eligible patients treated with new medicine (%)	20%	50%	60%	75%	80%
Number of patients treated with LIS in each year	3	8	11	16	19
Discontinuation rate	N/A	N/A	N/A	N/A	N/A
LIS medicine expenditure*	¶¶	¶¶	¶¶	¶¶	¶¶
AZT medicine expenditure with the displaced medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net financial saving	¶¶	¶¶	¶¶	¶¶	¶¶

Note: costs are based on 100% patient adherence as well as based on the licensed utilisation (i.e. on a treatment regimen of 28 days on-treatment followed by 28 days on-treatment resulting in a maximum of six 'on'/'off' treatment cycles per year).
LIS: levofloxacin inhalation solution AZT: aztreonam lysine
¶¶ Commercial in confidence information removed.

5.1.3 AWTTC critique

- [Commercial in confidence information removed.] The company have not provided scenario analyses with a range of discount values for the comparator. [Commercial in confidence information removed.] The analysis provided focuses solely on the difference in the comparator treatment cost. No other costs are considered in the analysis (e.g. differences in the costs of concomitant medications, routine resource use, hospitalisations etc.).
- The company estimates that levofloxacin will take an initial 20% market share from aztreonam lysine in the first year, increasing to 80% in year five based on improved convenience and increasing confidence. Lower uptake rates will inevitably alter the budget impact of levofloxacin.
- No sensitivity analyses are provided to explore the effect of uncertainty on the results.
- Collectively, the budget impact analysis provided by the company is subject to considerable uncertainty.

5.2 Comparative unit costs

Acquisition costs per 28 day course for different maintenance treatment regimens for chronic *P. aeruginosa* in patients with CF are described in Table 7.

Table 7. Examples of acquisition costs of maintenance treatment for *P. aeruginosa* in patients with CF

Regimens	Example doses	Approximate costs for 28 days
Levofloxacin (Quinsair®) Powder for nebuliser solution 240 mg	Twice a day over 28 days	£2,181.53 ¶¶
Aztreonam lysine (Cayston®) Powder for nebuliser solution 75 mg	3 times within 24 hours over 28 days (84 vials); including nebuliser handset	£2,181.53
Colistimethate sodium (Colomycin®) Powder for nebuliser solution	1–2 million units twice daily (£1.80 and £3.24 per 1 and 2 million unit vial)	£100.80–£181.44
Colistimethate sodium (Promixin®) Powder for nebuliser solution	1–2 million units twice to 3 times daily (£5.60 per 1-million units)	£313.60–£940.80
Colistimethate sodium (Colobreath®) Dry powder inhalation	1.66 million units per capsule twice a day, 56 capsule pack	£968.80 (including Turbospin® device)
Tobramycin (Bramitob®) Nebuliser solution 300 mg	One unit (300 mg in 4 ml) every 12 hours over 28 days	£1,187.00
Tobramycin (Tobi®) Nebuliser solution 300 mg	One unit (300 mg in 5 ml) every 12 hours over 28 days	£1,305.92
Tobramycin (Tobi®) Dry powder inhalation 28 mg	One capsule twice daily	£447.50 (including Podhaler™ device)
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,13,21-25]. Costs are based on BNF[17] list prices as of 15 June 2016, assuming vial wastage. Costs of administration are not included. This table does not imply therapeutic equivalence of medicines or the stated doses. ¶¶ Commercial in confidence information removed.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, levofloxacin (Quinsair®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration. It may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 8 June 2016
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The prevalence of the population for the full licensed indication of levofloxacin (Quinsair®▼) is reported to be 104 patients based on there being 216 patients aged ≥ 16 years with CF and 48.2% of adult patients with CF having chronic *P. aeruginosa*[8].

AWTTC consider levofloxacin (Quinsair®▼) to be eligible to be appraised as a medicine developed specifically for rare diseases as the full population of the licensed indication does not exceed the threshold of ≤ 5 patients in 10,000 (≤ 1,500 patients in Wales).

NMG/AWMSG will consider additional criteria (see Table 8) if they consider levofloxacin (Quinsair®▼) is a medicine developed specifically for rare diseases and the cost per QALY is above the normal thresholds applied

Table 8. Evidence considered by NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life, impacts on patients and their carers	CF is a life-limiting condition; the leading cause of mortality is progressive loss of lung function. Current therapies alleviate symptoms only and require time and effort that imposes a significant burden on patients' and their carers' quality of life.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	There are three other antibiotics available. The medicine would provide an additional antibiotic for rotating antibiotics to prevent resistance. It would also provide an additional treatment for patients with resistance antibiotics available.
Whether the medicine can reverse or cure, rather than stabilise the condition	This medicine does not reverse or cure the condition.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	The medicine does not bridge a gap to definitive therapy.
The innovative nature of the medicine	The medicine provides an alternative nebulised antibiotic treatment, but other antibiotic treatments are available.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	Levofloxacin can result in improved pulmonary function, reduced risk of hospitalisation, reduced time to exacerbation, and reduced risk of needing additional antibiotics. The company report this would positively impact on the societal burden in the indicated patient population. The company submission reports that in the UK in 2012, productivity losses (comprised of sick leave and early retirement costs) accounted for 12.8% of the total costs for CF patients[26]. The patients in the MPEX-209 trial that received LIS missed an average of 2.9 days of school/work/scheduled activity to worsened respiratory status, while TIS treated patients missed an average of 5.2 days[1].
Added value to the patient's family (e.g. impact on a carer or family life)	Reduced hospitalisations, exacerbations and pulmonary function are likely to add value to the patient's family.

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