Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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levofloxacin 240mg nebuliser solution (Quinsair®) SMC No. (1162/16)

Raptor Pharmaceuticals Europe B.V

10 June 2016 *(Issued 8 July 2016)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan equivalent process

levofloxacin (Quinsair®) is accepted for restricted use within NHS Scotland.

Indication under review: the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis.

SMC restriction: for use as a third line treatment option after colistimethate sodium (first line) and tobramycin (second line).

In a phase III open-label randomised study, levofloxacin was non-inferior to another inhaled antimicrobial for change in lung function, measured by relative change in forced expiratory volume in one second (FEV_1) percent predicted.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of levofloxacin. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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.

Dosing Information

The recommended dosage is 240mg (one ampoule) administered by inhalation twice daily.

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

Product availability date

12 July 2016. Levofloxacin inhalation solution meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Levofloxacin is a fluoroquinolone antibiotic that inhibits bacterial DNA gyrase and topoisomerase IV enzymes.[1] Levofloxacin is the first fluoroquinolone antibiotic to be formulated for use as an inhalation preparation. The submitting company has requested that SMC considers levofloxacin inhalation solution as a third line treatment option after colistimethate sodium (first line) and tobramycin (second line) in management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis (CF).

Evidence to support the marketing authorisation included two phase III, randomised controlled studies, MPEX-209 and MPEX-207, conducted in patients ≥12 years of age and weighing at least 30kg with CF, chronic airway infection with *Pseudomonas aeruginosa* and a forced expiratory volume in one second (FEV_1) between 25 and 85% predicted.[2]

MPEX-209 was an open-label study designed to compare the efficacy and safety of levofloxacin inhalation solution (levofloxacin) and tobramycin inhalation solution (tobramycin) in 282 patients who had received at least three 28-day courses of inhaled tobramycin in the 12 months prior to screening.[3] Patients were stratified by geographic region (USA versus non-USA), age (12 to 18 years versus >18 years), and FEV_1 percent predicted (<55% versus ≥55%) then randomised in a 2:1 ratio to receive levofloxacin 240mg twice daily or tobramycin 300mg twice daily for three cycles in a 28 days on/28 days off treatment pattern.[2,3] Patients continued their routine respiratory care and medicines; additional anti-pseudomonal medicines were only permitted if deemed necessary to treat a suspected exacerbation.[3]

The primary efficacy endpoint was relative change in FEV_1 percent predicted from baseline to day 28 measured in the intention to treat population.[3] A non-inferiority margin was pre-specified at -4%. The least squares mean relative change was 2.24% in the levofloxacin group (from baseline of 55%) and 0.38% in the tobramycin group (from baseline of 53%). The least squares mean relative difference (levofloxacin minus tobramycin) was 1.86% (95% Confidence Interval [CI]: -0.66 to 4.39), therefore non-inferiority was demonstrated.[2] The superiority analysis did not demonstrate a significant difference between the groups (p=0.15).[3] Selected secondary outcomes are presented in table 1; these numerically or statistically significantly favoured the levofloxacin group. There was no significant

difference between the groups for the absolute change in FEV_1 percent predicted from baseline to day 28; the least squares mean difference was 1.04% (95% CI -0.21 to 2.30), p=0.10. The change from baseline to day 28 in *Pseudomonas aeruginosa* sputum density numerically favoured the tobramycin group compared with the levofloxacin group; least squares mean difference 0.44 log_{10} colony forming units/gram (cfu/g, 95% CI: -0.01 to 0.88).[3]

Table 1: Selected secondary outcomes in full study population[3]

Outcome	levofloxacin group (n=189)	tobramycin group (n=93)	HR (95% CI), p value
Median time to first exacerbation	131 days	90 days	0.78 (0.57 to 1.07), p=0.15
Median time to administration of additional anti-pseudomonal antibiotics	141 days	110 days	0.73 (0.53 to 1.01), p=0.04
Proportion of patients hospitalised for a respiratory exacerbation over the 168 day study period	18%	28%	- p=0.04

HR: hazard ratio, CI: confidence interval

Quality of life was measured using the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), in which responses are converted to a 0 to 100 scale. Baseline scores for the two treatment groups were similar. Quality of life generally improved over the treatment period for patients in the levofloxacin group and generally worsened for patients in the tobramycin group; least squares mean change from baseline to day 28 was 1.88 and -1.31 respectively, least squares mean difference at day 28 was 3.19 (p=0.05). At the end of the study period, the results were similar for the two treatment groups.[3,5]

Patients initially enrolled in MPEX-209 who were clinically stable at day 168 could choose to receive three cycles of open-label levofloxacin inhalation solution as part of the single-arm MPEX-209 extension study. Uptake was low; of 144 patients eligible, only 88 enrolled and 15 discontinued before the end of the study period. Patients who had received tobramycin in MPEX-209 had a good response with the first cycle of levofloxacin and lesser responses with their second and third cycles, measured by FEV_1 percent predicted. Patients who had previously received three cycles of levofloxacin continued to respond in the fourth and fifth cycle but not with the sixth cycle.[2]

MPEX-207 was a double-blind study designed to compare the efficacy and safety of levofloxacin with placebo in 330 patients who had previously received at least three 28-day courses of an inhaled antimicrobial in the 12 months prior to screening.[2] Patients were stratified in the same manner as MPEX-209 then randomised in a 2:1 ratio to receive levofloxacin 240mg twice daily or placebo for one cycle in a 28 days on/28 days off treatment pattern.[2]

The primary efficacy endpoint was time to exacerbation. A pulmonary exacerbation was experienced by 55% (122/220) of patients in the levofloxacin group and 47% (52/110) of patients in the placebo group. The median time to exacerbation was 51.5 days in the levofloxacin group and 58 days in the placebo group, HR 1.33 (95% CI: 0.96 to 1.84), p=0.0715.[2] The least squares mean relative change in FEV_1 percent predicted at day 28 was 3.66% in the levofloxacin group (from baseline of 57%) and 1.24% in the placebo group (from baseline of 56%). The least squares mean relative difference (levofloxacin minus placebo) was 2.42% (95% CI: 0.53 to 4.31), p=0.012.[1] The least squares mean difference for the log change in *Pseudomonas aeruginosa* density from baseline to day 28 for the levofloxacin group compared with the placebo group was -0.63 (95% CI: -0.95 to -0.30), p=0.0002.[2]

Quality of life was also measured using the respiratory domain of CFQ-R and it generally improved over the treatment period for all patients; least squares mean change from baseline to day 28 was

4.66 and 4.94 respectively, the least squares mean difference at day 28 was 0.28 (95% CI: -2.3 to 2.85), p=0.8335.[2, 6]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Most patients enrolled in MPEX-209 reported at least one adverse event during the study (99% [180/182] and 100% [90/90] of patients treated with levofloxacin and tobramycin, respectively). Treatment emergent (TE) serious adverse events were reported by 22% of patients receiving levofloxacin and 32% of patients receiving tobramycin.[3] Discontinuation due to adverse events was low, 3.2% and 1.1% respectively.[3]

There was a notable difference in the proportion of patients reporting dysgeusia (taste distortion): 25% of patients treated with levofloxacin versus none of the patients taking tobramycin. The other adverse events reported in at least 5% more patients treated with levofloxacin versus tobramycin were cough (58% versus 53%), increased sputum (52% versus 44%), paranasal sinus hypersecretion (27% versus 20%) and sinus headache (19% versus 14%).[3]

The safety profile of levofloxacin administered systemically is well characterised. Recognised class effects of systemic fluoroquinolones such as nausea, arthralgia and tendonitis were uncommonly reported during the study.[3]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Cystic fibrosis is an unremitting, debilitating, life-limiting condition and lung damage following chronic *Pseudomonas aeruginosa* infection is a major contributor to morbidity and mortality. Improved treatment of chronic *Pseudomonas aeruginosa* infection has had a major influence on improving the median survival of patients with CF.[7] There are currently three antibiotics available for inhalation via a nebuliser to treat chronic *Pseudomonas aeruginosa* infection in patients with CF; colistimethate sodium, tobramycin and aztreonam lysine. Colistimethate sodium and tobramycin are also available as a dry powder inhaler. Intolerance or eventual lack of efficacy can occur with currently available therapies;[7] clinical experts consulted by SMC consider this is the area of unmet need in this therapeutic area. Levofloxacin inhalation solution meets SMC orphan equivalent criteria.

The submitting company has requested that SMC considers levofloxacin inhalation solution as a third line treatment option after colistimethate sodium (first line) and tobramycin (second line).

The MPEX-209 study demonstrated non-inferiority of levofloxacin compared with tobramycin measured by the surrogate primary outcome measure, FEV_1 percent predicted. This is the outcome recommended by the European Medicines Agency as it has been correlated with survival.[8] Most of the secondary outcomes numerically or statistically significantly favoured levofloxacin. The study did not demonstrate superiority of levofloxacin over tobramycin. The study was open-label due to the different nebuliser devices used and the primary outcome was measured after just one cycle, at day 28.[2] It is difficult to know how the requirement for three previous cycles of tobramycin has influenced the results. The response to tobramycin may be less with repeated treatment, possibly favouring levofloxacin. On the other hand, enrolled patients would already have demonstrated the ability to tolerate tobramycin potentially biasing against levofloxacin with regards to adverse events.[2] While the

company's proposed positioning is third line after both colistimethate sodium and tobramycin, not all patients had previously received colistimethate sodium although all patients had received tobramycin.

According to the European Public Assessment Report, many centres switch antibacterial agents with each cycle, leading to the low uptake for the MPEX-209 extension study. The low patient numbers and imbalance of patients who had previously received levofloxacin or tobramycin makes it difficult to interpret the findings.[2]

The MPEX-207 study did not show a benefit associated with levofloxacin measured by the primary direct health outcome, time to pulmonary exacerbation, or using the patient-reported respiratory domain of CFQ-R. It did show a modest benefit associated with levofloxacin measured by the secondary surrogate outcome FEV_1 percent predicted.[2] The company suggest that the imbalance in the mean number of exacerbations reported pre-study (2.0 versus 1.6) and proportion of patients who had previously experienced three or more exacerbations (34% versus 20%) may have biased against levofloxacin.[2] The placebo used in MPEX-207 was not taste matched which may have affected the blinding. The duration of the MPEX-207 study was a single cycle due to the inclusion of a placebo group.[2] Patients with chronic *Pseudomonas aeruginosa* infection now tend to be older; therefore, it was difficult to recruit patients less than 18 years to the study and over 80% of the study populations were adults. The marketing authorisation has therefore been granted in adults.[2, 7]

There is no direct evidence comparing levofloxacin with the most relevant comparator, aztreonam lysine. The company therefore conducted two Bayesian network meta-analyses (NMAs), a 4-week NMA including nine studies and a 24-week NMA including seven studies, to compare the clinical efficacy and safety of the inhalation antibiotics tobramycin, colistimethate sodium and aztreonam lysine with levofloxacin in patients (≥6 years) with CF and chronic *Pseudomonas aeruginosa* infection. The outcomes assessed were relative and absolute change in FEV_1 percent predicted, change in *Pseudomonas aeruginosa* density, CFQ-R respiratory symptoms score, hospitalisation, additional antibiotic use and withdrawal for any reason/lack of efficacy/any adverse events. Definitions of hospitalisation and additional antibiotic use varied across some of the studies. For most comparisons, the credible intervals were wide. Aztreonam lysine had the highest probability of being the best treatment for most outcomes in the two NMAs. The difference in previous exposure to tobramycin in the study populations and the correlation with reduced tobramycin efficacy suggests important heterogeneity within the NMAs. In addition, some of the studies included paediatric patients; it is unknown if this affected the results. An important limitation of the NMAs is that some of the study populations do not match the proposed positioning.

Levofloxacin inhalation solution is administered over a five minute period twice a day and aztreonam lysine is administered by inhalation over a two to three minute period three times a day.[1,9] Levofloxacin inhalation solution has a bitter taste which may make it unpleasant to use.[2]

While levofloxacin meets SMC orphan equivalent criteria, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of levofloxacin in the context of treatments currently available in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing levofloxacin to aztreonam lysine for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with CF. Levofloxacin is positioned for third line use after colistimethate sodium (first line) and tobramycin (second line). The results of the analysis were provided over a 3 year, 5 year and lifetime horizon. SMC experts consider aztreonam lysine to be the treatment most likely to be displaced in Scotland.

The clinical data used to support the assumption of comparable efficacy between treatments were taken from two NMAs (4-week and 24-week). Based on these analyses levofloxacin was considered by the company to be comparable to aztreonam lysine for most of the key outcome measures, with credible intervals overlapping. It should be noted the NMAs included two studies which compared levofloxacin to tobramycin (MPEX-209 and MPEX-207). There is no direct evidence comparing levofloxacin to aztreonam lysine.

The analysis included drug acquisition costs as well as overall CF, minor exacerbation, major exacerbation and transplantation costs. However, as non-drug costs are expected to be the same for both treatments, the analysis accounts only for differences in drug costs. A patient access scheme (PAS) is in place for aztreonam lysine and the analysis included an estimate of the PAS price for this medicine.

A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of levofloxacin. With the PAS, levofloxacin is a cost-effective treatment option.

Due to the limitations surrounding the NMAs, the assumption of comparable efficacy between levofloxacin and aztreonam lysine is uncertain. As noted in the clinical effectiveness section, considerable heterogeneity existed between patient populations in relation to previous treatment with inhaled tobramycin.

The Committee considered the benefits of levofloxacin in the context of its decision modifiers and agreed that, as levofloxacin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate modifier, the Committee accepted levofloxacin for restricted use in NHS Scotland.

Summary of patient and public involvement

The following information reflects the views of the specified patient group.

- A submission was received from the Cystic Fibrosis Trust which is a registered charity.
- The patient group has received <3% pharmaceutical company funding in the past two years, but none from the submitting company.
- Cystic fibrosis (CF) is a chronic, progressive disease, characterised by repeated, potentially life threatening pulmonary infections (exacerbations). This causes irreversible scarring of the lungs and a decline in lung function over time which results in respiratory failure or the need for a lung transplant. CF patients endure repeated hospitalisations, missed days from school and work, and significant morbidity and mortality.
- Existing antibiotic treatments are limited by emerging resistance with loss of response, allergic reactions and limited tolerability for some patients. Even with an optimal treatment regimen, people with CF will experience frequent exacerbations. Intravenous antibiotic therapy is often required to treat infection to help minimise further damage to the lungs.
- Levofloxacin is a broad spectrum inhaled antibacterial agent with a different mechanism of action to other inhaled antibiotics so it may confer additional benefit for CF patients who continue to suffer from declining lung function and pulmonary exacerbations.

Additional information: guidelines and protocols

Published guidelines on the use of inhaled antibiotics for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with CF predate the approval of levofloxacin inhalation solution for this indication.

The National Institute of Health and Care Excellence conducted a multiple technology appraisal (TA276) reviewing colistimethate sodium and tobramycin dry powders for inhalation for treating *Pseudomonas aeruginosa* lung infection in CF in March 2013.[10] Healthcare Improvement Scotland has advised that these recommendations are valid for NHSScotland.

- Colistimethate sodium dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with CF only if:
    - the patient would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered; and
    - the manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.
- Tobramycin DPI is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with CF only if:
    - nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response; and
    - the manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

The European Cystic Fibrosis Society updated their consensus statement for the treatment of lung infection in patients with CF in 2012.[7] There is still considered to be a need for additional antibiotic choices for the management of CF airways disease due to intolerance or lack of efficacy. The guideline discusses the inhaled antibiotics colistimethate sodium, tobramycin and aztreonam lysine, but does not make recommendations for the use of one in preference over another.

Additional information: comparators

Aztreonam lysine nebuliser solution is the most relevant comparator considering the company's requested positioning as a third line treatment option after colistimethate sodium (first line) and tobramycin (second line).

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28-day cycle (£)
Levofloxacin	**240mg inhaled via a nebuliser twice a day for 28 days followed by 28 days off treatment**	***CiC***
Aztreonam lysine	75mg inhaled via a nebuliser three times a day for 28 days followed by 28 days off treatment	2,182

Doses are for general comparison and do not imply therapeutic equivalence. Levofloxacin cost from company submission, all other costs from MIMS on 24/3/2016. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 35 patients in year 1, rising to 56 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Raptor Pharmaceuticals Europe B.V. Summary of Product Characteristics. Levofloxacin (Quinsair) nebuliser solution. 26 March 2015.

2. European Medicines Agency. Assessment report: levofloxacin Quinsair EMEA/H/C/002789/0000. 18 December 2014.

3. Elborn JS, Geller DE, Conrad D, Aaron SD, Smyth AR, Fischer R*, et al.* A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients. Journal of Cystic Fibrosis. 2015;14(4):507-14.

4. *Commercial in Confidence** .

5. *Commercial in Confidence**.

6. *Commercial in Confidence**.

7. Doring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. Journal of Cystic Fibrosis. 2012;11(6):461-79.

8. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the clinical development if medicinal products for the treatment of cystic fibrosis. 2008.

9. Gilead Sciences Ltd. Summary of Product Characteristics. Aztreonam lysine (Cayston) 75mg powder and solvent for nebuliser solution Last updated 4 September 2015 www.medicines.org.uk.

10. National Institute for Health and Care Excellence. TA276: Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis. 2013.

This assessment is based on data submitted by the applicant company up to and including 11 May 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG,

established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.