CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

LEVOFLOXACIN INHALATION SOLUTION
(Quinsair — Raptor Pharmaceuticals Inc.)
Indication: Cystic Fibrosis with Chronic Pulmonary *Pseudomonas Aeruginosa* Infections

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that levofloxacin inhalation solution (LIS) be reimbursed for the management of cystic fibrosis (CF) in patients 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* (*P. aeruginosa*) infections, if the following conditions are met:

Conditions:
- The drug is prescribed by a clinician with experience in the diagnosis and treatment of CF.
- The drug is not used in combination with another inhaled antibiotic(s) to treat pulmonary *P. aeruginosa* infections, either concurrently or for antibiotic cycling during off-treatment periods.
- Price of the drug does not exceed that of the least expensive available indicated inhaled antimicrobial alternative.

Reasons for the Recommendation:
1. In one open-label randomized controlled trial (RCT) (MPEX-209 [N = 282]), LIS was non-inferior to tobramycin inhalation solution (TIS) in terms of change in per cent predicted forced expiratory volume in one second ($ppFEV_1$) from baseline to day 28. As well, two placebo-controlled RCTs (MPEX-204 [N = 151] and MPEX-207 [N = 330]) demonstrated that treatment with LIS was associated with a statistically significant greater improvement in $ppFEV_1$ from baseline to day 28 compared with placebo.
2. There are no studies currently available to directly compare LIS to alternative inhaled antimicrobials (other than TIS) for the treatment of patients with CF and pulmonary *P. aeruginosa* infection, such as aztreonam inhalation solution. The conclusions of a manufacturer-provided network meta-analysis (NMA) comparing LIS with tobramycin (inhalation solution and powder), aztreonam, and colistimethate are uncertain due to important limitations in the NMA methods and source data.
3. At the submitted price of $4,045.14 per 28-day pack, it is unlikely that LIS is cost-effective compared with TIS or powder. The cost-effectiveness compared with aztreonam cannot be estimated as the relative efficacy of LIS when compared to aztreonam is uncertain.

Of Note:
The Health Canada indication for LIS does not identify its place in therapy. However, CDEC heard from a clinician expert in the diagnosis and treatment of CF that LIS will most likely be used as second-line treatment after inhaled tobramycin for pulmonary *P. aeruginosa* infections.

Research Gaps:
CDEC discussed the absence of evidence regarding the following:

- Long-term comparative evidence including patient-important outcomes such as acute pulmonary exacerbations, health-related quality of life, daily activities, and adverse events.
- Evidence from the RCTs for an administration advantage of LIS compared with other inhaled antibiotics.
- Evidence from RCTs on antibiotic cycling (i.e., use of LIS during off-treatment periods of other inhaled antibiotics, especially tobramycin).

Background:
LIS is a fluoroquinolone antibiotic that has anti–*P. aeruginosa* activity. LIS has a Health Canada–approved indication for the management of CF in patients 18 years or older with chronic pulmonary *P. aeruginosa* infections. Patients administer 240 mg by inhalation twice daily, taken in alternating cycles of 28 days on treatment followed by 28 days off.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of three RCTs of LIS, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with CF and their caregivers.

Patient Input Information:
Cystic Fibrosis Canada (CF Canada) and the Patient Family Advisory Board for the Cystic Fibrosis Program at St. Michael's Hospital in Toronto (PFAB) responded to the CDR call for patient input. Information was obtained from surveying members of CF Canada and the personal experience of several PFAB members. The following is a summary of information provided by the patient groups:

- CF can have a negative impact on many aspects of patients' lives, and those who are affected spend at least two hours a day on various therapies, take as many as 40 pills a day, and are sometimes forced to spend about two weeks in hospital to manage exacerbations. CF affects decisions about education, career, travel, relationships, and family planning.
- Patients emphasized concern over increasing antibiotic resistance, and their apprehension about "running out of antibiotics to turn to" to treat pulmonary infections.
- Patient input did not report any experience from patients who had used LIS. Nevertheless, patients expect that the administration of LIS will be more convenient and time-saving than the other available inhaled antibiotic treatments.

Clinical Trials
The systematic review included three RCTs of patients with CF who had chronic pulmonary *P. aeruginosa* infections: MPEX-204 (N = 151), MPEX-207 (N = 330), and MPEX-209 (N = 282).

MPEX-204 and 207 were double-blind superiority studies, while MPEX-209 was an open-label non-inferiority trial. MPEX-204 was a phase II dose-finding trial that compared the efficacy, safety, and tolerability of three dosage regimens of LIS (120 mg once daily, 240 mg once daily, and 240 mg twice daily) administered over 28 days, compared with placebo. MPEX-207 was a phase III trial designed to evaluate the efficacy and safety of LIS 240 mg twice daily administered over 28 days compared with placebo. MPEX-209 was a non-inferiority study that compared the safety and efficacy of LIS 240 mg twice daily and TIS 300 mg twice daily when administered over three cycles of 28 days on and off treatment.

Only evidence related to the Health Canada–approved dosing regimen for LIS was considered.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: disease progression in terms of change from baseline in $ppFEV_1$, pulmonary exacerbations, health-related quality of life, hospitalization, and missed work and/or school days.

Primary outcomes of the included trials were sputum microbiology in MPEX-204, time to pulmonary exacerbation in MPEX-207, and change in $ppFEV_1$ from baseline in MPEX-209. The primary efficacy analyses were based on 28 days of treatment in the three included trials. Health-related quality of life was evaluated using Cystic Fibrosis Questionnaire–Revised (CFQ-R). None of the included studies was designed to evaluate patients' survival, and there were no deaths reported.

Efficacy

- LIS was associated with a statistically significant greater improvement in absolute change in $ppFEV_1$ from baseline to day 28 compared with placebo in MPEX-207: least squares (LS) mean difference was 1.31% (95% confidence interval [CI], 0.27% to 2.34%). However, there was no statistically significant difference between LIS and TIS with respect to absolute change in $ppFEV_1$ from baseline to day 28: LS mean difference was 1.04% (95% CI, –0.21% to 2.30%) in MPEX-209. Absolute change from baseline in $ppFEV_1$ was not assessed in MPEX-204.
- LIS was associated with a statistically significant greater improvement in relative change in $ppFEV_1$ from baseline to day 28 compared with placebo in MPEX-204 and 207: LS mean differences were 10.9% (95% CI, 4.6% to 17.3%) and 2.42% (95% CI, 0.53% to 4.31%), respectively. In MPEX-209, the relative change from baseline showed that LIS was non-inferior compared with TIS based on a –4% non-inferiority margin: the LS mean difference between groups after 28 days of treatment was 1.86% (95% CI, –0.66% to 4.39%).
- In MPEX-207, LIS was associated with more exacerbation events than placebo, but the difference was not statistically significant. In MPEX-209, however, LIS was associated with fewer exacerbation events than TIS, but the difference between treatments was not statistically significant. MPEX-204 did not include pulmonary exacerbations as an outcome.
- In MPEX-204 and MPEX-207, LIS-treated patients had a numerically higher increase in health-related quality of life, measured as CFQ-R scores from baseline to day 28, than placebo patients, but the difference between LIS and placebo was not statistically significant. In MPEX-209, however, LIS-treated patients showed a statistically significant improvement in CFQ-R scores from baseline to day 28 compared with TIS (1.88 versus –1.31); the LS mean difference was 3.19 points (95% CI, 0.05 to 6.32). The minimal clinically important difference for patients with stable disease is 4.0 points and for patients with exacerbations 8.5 points.

- MPEX-207 and 209 reported hospitalizations and missed days of school/work/or daily activities. No statistically significant differences between LIS and placebo or TIS were reported for these outcomes.

Harms (Safety and Tolerability)

- Serious adverse events were similar between LIS and placebo: 8% versus 10.8% in MPEX-204 and 9.6% versus 10% in MPEX-207. In MPEX-209, lower rates of serious adverse events were reported by LIS patients (22%) compared with TIS patients (32.2%). In the three trials, the most common serious adverse event was disease progression.
- Overall, there were 84.6% versus 75.7% of patients reporting adverse events in MPEX-204 in LIS and placebo groups, respectively. In MPEX-207, 97.7% of LIS group reported adverse events compared with 98.2% of the placebo group. In MPEX-209, 98.2% of LIS group reported adverse events compared with 96.9% in the TIS group.
- In MPEX-204, there were fewer LIS patients who discontinued study drug due to adverse events than placebo (5.1% versus 10.8%). In MPEX-207 and 209, however, there was a higher frequency of treatment discontinuation due to adverse events in LIS groups than placebo (5% versus 1.8%) and TIS (6.3% versus 1.1%).
- The studies were too short in duration and likely had too small of a sample size to assess the risk of adverse events that have been associated with fluoroquinolones, such as tendon injury.

Cost and Cost-Effectiveness

LIS is available at a manufacturer-submitted price of $4,045.14 per 28-day pack of 56 ready to use 3 mL ampoules containing 240 mg LIS.

The manufacturer submitted a cost-utility analysis (CUA) assessing LIS compared with aztreonam for the treatment of chronic *P. aeruginosa* lung infection in adults with CF. Supplemental CUAs comparing LIS with tobramycin inhaled powder and TIS were also presented. Analyses were undertaken from the perspective of a Canadian public payer over a lifetime time horizon (up to 79 years). The CUAs were developed based on a published Markov model which simulated disease progression as determined by a change in lung function (based on $ppFEV_1$). The probability of transitioning between $ppFEV_1$ health states was based on data from a manufacturer-sponsored NMA for the comparisons with aztreonam and tobramycin powder, and from the MPEX-209 study for the comparison with TIS.

CDR identified several limitations with the manufacturer's submission, including: the results of the manufacturer's NMA were associated with substantial uncertainty; the exacerbation rates from trials are likely to differ from those observed in practice due to differences in the definitions of exacerbation; and, post-transplantation utility values failed face validity while $ppFEV_1$ health state utility values were sourced from the UK which has an impact on the applicability to a Canadian context.

The NMA was judged to be associated with a level of uncertainty that prevented its use for CDR reanalyses. Data from the MPEX-209 study comparing LIS with TIS were used instead to inform the transition probabilities for LIS compared with both tobramycin powder and TIS. In addition, an alternative utility value was considered post transplantation. Based on CDR reanalyses, an incremental cost-utility ratio of $358,486 per quality-adjusted life-year (QALY) for LIS compared with tobramycin powder, and of $852,854 per QALY for LIS compared with TIS were estimated. For the comparison of levofloxacin versus aztreonam, in the absence of suitable comparative

effectiveness data, only the drug cost could be compared. The drug acquisition cost of LIS is the same as aztreonam.

Assuming equal efficacy for the compared interventions, a price reduction for LIS of 62% (based on the submitted price) is required to be equal to the daily cost of tobramycin (Tobi, generic, 300 mg/mL solution for inhalation, based on the Ontario Drug Benefit formulary price). A price reduction for LIS of between 54% and 77% is required for the daily cost of LIS to be equal to the daily cost of colistimethate sodium (Colobreathe, 150 mg vial, based on the Alberta Drug formulary price, at a recommended daily dose of 2.5 mg/kg to 5.0 mg/kg, assuming a patient weight of 60 kg).

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

October 19, 2016 Meeting:

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary reimbursement recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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