Common Drug Review

Pharmacoeconomic Review Report

November 2016

Drug	Levofloxacin solution for inhalation (Quinsair)
Indication	The management of cystic fibrosis in patients 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections
Reimbursement request	As per indication
Dosage form (s)	Inhalation solution 240 mg/2.4 mL (100 mg/mL)
NOC date	09-06-2015 (initial NOC) 05-01-2016 (transfer of DIN)
Manufacturer	Raptor Pharmaceutical Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
CF	cystic fibrosis
CIHI	Canadian Institute for Health Information
EAP	expanded access program
FEV_1	forced expiration volume in one second
ICUR	incremental cost-utility ratio
K-M	Kaplan-Meier
NMA	network meta-analysis
PCE	patient cost estimator
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
TIP	tobramycin inhalation powder
TIS	tobramycin inhalation solution

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Levofloxacin (Quinsair) 240 mg/2.4 mL solution for inhalation
Study Question	"To conduct an economic evaluation of [levofloxacin] (Quinsair) compared with aztreonam (Cayston) for the treatment of chronic *Pseudomonas aeruginosa (P. aeruginosa)* lung infection in CF patients in Canada. Additionally, the cost-effectiveness of LIS was evaluated as compared with (tobramycin solution for inhalation) and tobramycin in dry powder (TOBI Podhaler)."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients 12 years or older with a diagnosis of CF and FEV_1 of 25% or greater, but a predicted value of 85% or less, who are clinically stable and chronically infected with *P. aeruginosa* who had previously used cycled inhaled antibiotic (per the MPEX-209 trial population). A subgroup analysis of the trial's population was provided for patients 18 years or older, per the Health Canada–approved indication.
Treatment	Levofloxacin 240 mg administered by inhalation twice daily, taken in alternating cycles of 28 days on treatment followed by 28 days off treatment
Outcome	QALYs
Comparators	Aztreonam 75 mg administered by inhalation three times per day, taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. Supplemental analyses were provided assessing levofloxacin against tobramycin powder for inhalation and tobramycin solution for inhalation using the same treatment regimen; alternating cycles of 28 days on and off treatment.
Perspective	Canadian publicly funded health care system
Time Horizon	Lifetime (up to 79 years)
Results	ICUR for levofloxacin for the Health Canada indication (patients 18 years or older) versus: • aztreonam = $3,101 per QALY The manufacturer provided supplemental analyses presenting the ICUR for levofloxacin compared with: • tobramycin powder for inhalation = $58,840 per QALY • tobramycin solution for inhalation = $918,269 per QALY
Key Limitations	CDR identified the following key limitations with the manufacturer's submitted economic evaluation: • The manufacturer's base-case analysis did not consider all relevant comparators, e.g., tobramycin solution and tobramycin powder. As such, full analyses (including probabilistic analyses) were only provided compared with aztreonam, and sequential analyses could not be conducted. • The treatment-specific transition probabilities derived from an NMA were associated with substantial uncertainty and overestimate the benefit of levofloxacin versus aztreonam. CDR reanalyses were undertaken considering the direct evidence from the MPEX-209 trial, which compared levofloxacin with tobramycin, and in the absence of robust evidence, conducted an exploratory analysis assuming equal efficacy for levofloxacin and aztreonam. • The modelling of exacerbations was associated with uncertainty, due to differences between definition of exacerbation in Canadian clinical practice and the MPEX-209 clinical trial, and the uncertainty associated with the manufacturer's NMA from which some of this data were derived. In the absence of a more appropriate comparative data source, CDR reanalyses applied the MPEX-209 exacerbation rates for levofloxacin, tobramycin solution, and also to tobramycin powder, and assumed the same exacerbation rate for levofloxacin and aztreonam.

	• The utility value for the post-transplant health state does not appear to meet face validity. CDR undertook reanalyses using the utility value for the mild disease health state for the post-transplant health states.
CDR Best Estimates	Based on the transition probabilities derived from a post-hoc analysis of the MPEX-209 trial, and revised utility values and exacerbation rates, the ICURs for levofloxacin compared with tobramycin are reported as follow: • tobramycin powder for inhalation = $358,486 per QALY • tobramycin solution for inhalation = $852,854 per QALY CDR undertook an exploratory analysis assuming equivalent efficacy for levofloxacin compared with aztreonam. Levofloxacin is associated with no differences in QALYs, and no difference in costs compared with aztreonam.

CDR = CADTH Common Drug Review; CF = cystic fibrosis; FEV_1 = forced expiration volume in one second; ICUR = incremental cost-utility ratio; LIS = levofloxacin inhalation solution; NMA = network meta-analysis; QALY = quality-adjusted life-years.

EXECUTIVE SUMMARY

Background

Levofloxacin (Quinsair) is the first inhaled fluoroquinolone and a third class of inhaled antibiotics for the long-term management of *Pseudomonas aeruginosa* (*P. aeruginosa*) infection in patients with cystic fibrosis (CF). Levofloxacin was approved by Health Canada in 2015 for use for the above indication in adults.[1] The manufacturer requested reimbursement of levofloxacin as per the Health Canada indication.[2]

Levofloxacin is available as 28-day pack containing 56 ready-to-use ampoules. Each ampoule is 3 mL in size and delivers 2.4 mL or 240 mg of levofloxacin. The Zirela Nebulizer Handset, packaged in its own box with the manufacturer's instruction for use, is included in each pack of levofloxacin. Levofloxacin is administered as a twice daily inhalation for 28 days on treatment, followed by 28 days off treatment.[2] The product monograph notes that the efficacy and safety of levofloxacin has not been established beyond six months of treatment.[1] The manufacturer submitted levofloxacin at the marketed price of $4,045.14 per 28-day pack.[2]

The manufacturer undertook two cost-utility analyses (CUAs) to determine the cost-effectiveness of levofloxacin compared with aztreonam for the treatment of chronic *P. aeruginosa* lung infection in CF patients in Canada over a lifetime time horizon. One analysis was based on the population in the MPEX-209 trial, which included patients under 18 years of age (for which levofloxacin is not indicated); and the other analysis was based on the adult subgroup of patients that fulfill the Health Canada indication. The manufacturer provided supplemental CUAs comparing levofloxacin solution with tobramycin solution for inhalation and tobramycin in dry powder, though all analyses were provided in separate economic models for information purposes only.[3] The CUAs were developed based on an earlier model by Tappenden et al., modified to the Canadian publicly funded health care system perspective.[4] The model simulates the disease progression of patients with CF as determined by a change in lung function, with the potential for lung transplantation, and death. Forced expiration volume in one second (FEV_1) % predicted (a comparison of the patient's FEV_1 with the predicted values of healthy patients with similar age, weight, and height)[5] was used as a "surrogate for lung function."[1] Patients enter the model in one of three health states with different levels of lung function based on FEV_1% predicted, and can transition among these states, or to transplant/post-transplant or death health states (Figure 1). The probability of transitioning between FEV_1 health states was based on data from a network meta-analysis (NMA)[6] of 24-week with studies comparing levofloxacin to other inhaled treatments (including aztreonam and tobramycin powder for inhalation) or a head-to-head trial comparing levofloxacin with tobramycin solution for inhalation (MPEX-209).[3,7,8] A consideration of natural history was not applied as patients in the models and trials assessed were receiving treatment with one of the inhaled anti-pseudomonal drugs. Transition probabilities for the transplantation and mortality health states were informed from the published literature.[4,9] Patients transitioned among the health states during 24-week period (cycle), which was reported as the time required for a patient to receive three courses of treatment. After one treatment cycle, patients could stay in the same FEV_1 state, improve FEV_1, or worsen. Only patients in the lowest FEV_1 state could undergo transplantation. Mortality rate was affected by age and health state. The model accounted for health-state specific probabilities for exacerbations while in the FEV_1 states. Patients who move out of the FEV_1 states no longer receive active treatment with levofloxacin, aztreonam, or tobramycin.[3] Quality of life data were not reported from the MPEX-209 study, thus the manufacturer obtained utility values from previously published values in the UK.[9-11] Drug, event, and

health state cost information was sourced from provincial formularies, the Canadian Institute for Health Information, expert opinion, and published literature.[12,13]

The incremental cost-utility ratio (ICUR) for levofloxacin compared with aztreonam for the management of *P. aeruginosa* infection in adult patients with CF (as per the Health Canada indication) was $3,101 per additional quality-adjusted life-year (QALY). The supplemental analyses assessing levofloxacin in adult patients with CF (as per the Health Canada indication) showed the ICURs for levofloxacin compared with tobramycin powder for inhalation ($58,840 per QALY) or tobramycin solution for inhalation ($918,269 per QALY) were substantially higher. Based on the trial population (including patients younger than 18 years of age), the ICURs were slightly higher in all analyses. The manufacturer undertook sensitivity analyses, which indicated that the model results were sensitive to the hazard ratio for mortality, CF costs, post-transplant costs, and distribution of patients based on baseline FEV_1 health state. A probabilistic sensitivity analysis that used 2,000 simulations for the population 18 years or older indicated there was a 99.2% probability that levofloxacin would be cost-effective compared with aztreonam at a willingness to pay of $100,000 per QALY.[3]

Summary of Identified Limitations

CDR noted substantial uncertainty associated with the manufacturer's economic analyses and the quality of the evidence provided. Treatment effect, assessed through patients transitioning between FEV_1-based health states and the potential for exacerbation events, was derived from an NMA for the comparison of levofloxacin with aztreonam and levofloxacin with tobramycin powder, and from a post-hoc analysis of head-to-head MPEX-209 trial data for levofloxacin with tobramycin solution. The CADTH Common Drug Review concluded that the results of the NMA were associated with substantial uncertainty given the limitations identified with the methodological rigour of it, while the data from the MPEX-209 trial could not be verified. CDR noted that the transition probabilities for levofloxacin differed depending on whether the NMA or direct trial data were used, and were unlikely to remain constant throughout the model as assumed by the manufacturer. In the absence of better evidence, CDR considered the direct head-to-head trial provided a higher level of evidence and may be more relevant for the CDR reanalyses that assess levofloxacin with both tobramycin solution and tobramycin powder.

Given the uncertainty associated with the NMA and data availability, CDR considered an exploratory scenario where levofloxacin was equivalent to aztreonam, although this assumption is associated with uncertainty. In addition, although the manufacturer provided analyses of levofloxacin with tobramycin powder and tobramycin solution as supplemental analyses, these analyses should have been presented as part of the base-case analysis given the broad indication approved by Health Canada. As these analyses were provided separately with different data sources, CDR could not consider these treatments in a sequential analysis.

CDR also noted that the utility values were associated with uncertainty. The manufacturer assumed that upon receipt of transplantation, patients would improve to a quality of life greater than they would have if the patient had mild disease (FEV_1 > 70% predicted), which does not appear to meet face validity. Feedback from the CDR clinical expert supported CDR's assessment, indicating that the post-transplant utility value do not take into account the additional risks that the transplant leads to (e.g., developing infections, lymphoproliferative disease, and diabetes). CDR undertook reanalyses assuming the post-transplant utility value was equivalent to the mild FEV_1 health state value. Additionally, the base health states, based on the FEV_1% predicted, were sourced from the UK, which may be associated with generalizability issues.

Conclusions and Key Results

CDR determined that the relevant comparators for levofloxacin were aztreonam, tobramycin powder, and tobramycin solution for the treatment of *P. aeruginosa* in adult patients with CF. As these comparators could not all be considered simultaneously within a run of the model given the model structure, results compared with levofloxacin were presented separately. CDR attempted to address the key limitations by prioritizing the direct head-to-head evidence, given the uncertainty associated with the NMA submitted by the manufacturer.

Based on the transition probabilities derived from the post-hoc analysis of the MPEX-209 trial and revised utility values and exacerbation rates, the CDR results indicated that levofloxacin is associated with an ICUR of $358,486 per QALY compared with tobramycin powder, and an ICUR of $852,854 per QALY compared with tobramycin solution. Given the uncertainty regarding the comparative clinical efficacy and safety, and the broad product indication, the true cost-effectiveness of levofloxacin and how it could be used in clinical practice is uncertain.

Should levofloxacin and aztreonam be found to be similar efficacious, levofloxacin is equal in cost to the list price of aztreonam.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC ECONOMIC SUBMISSION

The manufacturer submitted two base-case economic analyses (cost-utility analyses; CUAs) that compared levofloxacin with aztreonam for the management of chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) lung infection in patients with cystic fibrosis (CF). The CUAs were undertaken for two populations based on the MPEX-209 study (levofloxacin versus tobramycin solution), one assessing the full patient set (including patients 12 years and older), and the other assessing a subgroup of adult patients (18 years and older) only, asper the Health Canada indication.[3]

The manufacturer provided additional cost-effectiveness analyses of levofloxacin compared with tobramycin powder for inhalation, and tobramycin solution for inhalation separately, based on the CADTH feedback during the pre-submission meeting, though the manufacturer considered these as supplemental analyses for information purposes only. These additional analyses were also reported for the two patient populations assessed by the base case where the data were available.[3]

The CUAs were developed based on an earlier model designed and reported by Tappenden et al.[4] and modified to the Canadian publicly funded health care system perspective. The model simulates disease progression of CF patients with chronic *P. aeruginosa* infection as determined by a change in lung function, with the potential for lung transplantation, and death. Forced expiration volume in one second [FEV_1] % predicted (a comparison of the patient's FEV_1 with the predicted values of healthy patients with similar age, weight, and height) was used as a surrogate for lung function. The model has six health states between which patients transition every 24 weeks (cycle time). This time period was used as this was the duration of the study, and the time required for patients to receive a full course of treatment – three sets of four weeks on treatment, four weeks off treatment. The health states were comprised of: three health states based on lung function, as determined by FEV_1% predicted; one state for transplantation, one state for post-transplantation, and an absorbing health state for death (Figure 1). Only patients in the lowest FEV_1 state could undergo transplantation.[3]

Patients enter the model in one of the three FEV_1% predicted health states on levofloxacin or the comparator treatment, from which point on they have a probability of transitioning between these states, or to transplant/ post-transplant, or death health states. The probability of transitioning between FEV_1 health states was based on data from a network meta-analysis (NMA)[6] of 24-week studies comparing levofloxacin with other inhaled treatments (including aztreonam and tobramycin powder for inhalation) or a post-hoc analysis of a head-to-head trial comparing levofloxacin with tobramycin solution for inhalation (MPEX-209).[3,7,8] Transition probabilities for the transplantation and mortality health states were informed from the published literature.[4,9] Mortality rate was effected by age and health state. The model accounts for health-state specific probabilities for exacerbations while in the FEV_1 states; this was based on Kaplan-Meier estimates. The model assumes there is no relationship between a major exacerbation event and FEV_1 level or treatment. Patients who move out of the FEV_1 health states no longer receive active treatment with levofloxacin, aztreonam, or tobramycin.[3]

The manufacturer sourced utility values from previously published values from the UK for the health states, as well as disutility values due to exacerbations; the values were derived from online survey's and studies that measured utilities.[9-11] The manufacturer indicated that there were utility values from

the Canadian context for the post-transplant health states, which were tested in sensitivity analyses.[13] It was assumed that the utility decrement for an exacerbation would impact patients for a 10-week period.

Drug costs were sourced from the manufacturer (reference drug) and provincial formularies (comparators). Health state costs were sourced from published literature that reported Canadian costs,[12,13] extrapolated over a longer time horizon where required, and inflated to 2015 Canadian dollars. Exacerbation costs were determined from expert opinion (regarding resource use), and costs reported by provincial schedules and the Canadian Institute for Health Information.[14,15] A 5% discount rate on both costs and outcomes was applied per the CADTH Economic Evaluation Guidelines.[16]

2. MANUFACTURER'S BASE CASE

The results of the manufacturer's base-case economic analyses for both assessed populations indicated the incremental cost-utility ratio (ICUR) per additional quality-adjusted life-year (QALY) gained for levofloxacin versus aztreonam was low (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE-CASE ANALYSES

	Total Costs	Incremental Cost of Levofloxacin	Total QALYs	Incremental QALYs of Levofloxacin	Incremental Cost per QALY
Subgroup: 18 years or older					
Aztreonam	$298,306		4.896		
Levofloxacin	$300,499	$2,193	5.604	0.707	$3,101
Full population					
Aztreonam	$319,531		5.343		
Levofloxacin	$322,041	$2,510	5.961	0.618	$4,061

QALY = quality-adjusted life-year.

However, when assessing the comparative cost-effectiveness of levofloxacin with tobramycin powder for inhalation and tobramycin solution for inhalation, the ICURs reported by the manufacturer were substantially higher than the base-case comparison; the analysis of levofloxacin with tobramycin solution for inhalation based on the head-to-head trial found levofloxacin was decidedly not cost-effective at conventionally accepted thresholds (Table 3).

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S SUPPLEMENTAL ANALYSES

Comparison	Patient Population	Incremental Cost of Levofloxacin	Incremental QALYs of Levofloxacin	Incremental Cost per QALY
Levofloxacin vs. TPI	Subgroup: 18 years+	$51,415	0.874	$58,840
	Full population	$54,246	0.798	$67,966
Levofloxacin vs. TSI	Subgroup: 18 years+	$125,511	0.137	$918,269
	Full population	$133,111	0.131	$1,016,770

QALY = quality-adjusted life-year; TPI = tobramycin powder for inhalation; TSI = tobramycin solution for inhalation.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer undertook various sensitivity analyses on the base-case analyses comparing levofloxacin with aztreonam, indicating the following parameters had a moderate impact on the ICUR: mortality hazard ratio, CF costs, post-transplant costs, and distribution for FEV_1. The manufacturer's probabilistic sensitivity analysis (PSA) on the Health Canada population indicated levofloxacin was likely to be cost-effective compared with aztreonam at a willingness to pay of $100,000 per QALY (99.2% probability).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CADTH Common Drug Review CDR) identified several limitations with the manufacturer's pharmacoeconomic submission in the context of requesting reimbursement of levofloxacin for the treatment of *P. aeruginosa* infections in adult patients with CF.

- **Relevant comparators were not considered in manufacturer's base-case analysis:** The manufacturer's base case compared levofloxacin with aztreonam. The manufacturer provided supplemental analyses comparing levofloxacin with tobramycin powder and tobramycin solution based on feedback from CADTH at the pre-submission meeting, but stated that these were provided "as additional information" only. The manufacturer did not provide an analysis assessing the cost-effectiveness of levofloxacin compared with colistin. Feedback from the CDR clinical expert indicated the following treatments may be considered relevant comparators for levofloxacin given the broad indication: tobramycin powder, tobramycin solution, aztreonam, and colistin. However, as inhaled colistin is not recommended in Canada, and given its low use in practice, it was judged appropriate to not assess it against levofloxacin. CDR considered the comparisons of levofloxacin with tobramycin as relevant for decision-making, in addition to the comparison with aztreonam. CDR was unable to undertake a sequential analysis of the treatments as the analyses were provided in different models, and the data differed between models.
- **Substantial uncertainty with validity of transition probabilities:** The manufacturer derived transition probabilities for the comparison of levofloxacin versus tobramycin solution from post-hoc analysis of data from the MPEX-209 trial,[3,7] and derived transition probabilities for the other comparisons (versus aztreonam and versus tobramycin powder) from a network meta-analysis (NMA).[6] CDR noted transition probabilities for levofloxacin vary noticeably based on the source (NMA or MPEX-209 trial); using the NMA transition probabilities, the results indicate more QALYs, less exacerbations, and substantially more time in the milder FEV_1 states for levofloxacin. The transition probabilities for tobramycin solution and tobramycin powder differed noticeably; however literature has previously indicated similarity between the two options.[17,18] The CDR appraisal of the NMA (located in the CDR Clinical Study Report) identified a number of important limitations that make it difficult to conclude that differential in-treatment effects between the inhaled antibiotics (as issues with homogeneity, transitivity, and consistency), were not clearly and explicitly met or addressed. CDR considered it appropriate to apply transitions for tobramycin solution based on the MPEX-209 trial to tobramycin powder. Further, given the uncertainty associated with the transitions for aztreonam from the NMA, CDR undertook an exploratory analysis assuming equivalent efficacy for levofloxacin and aztreonam. Finally, the model assumes constant transitions over a lifetime; that is, constant levels of effect over time, which may overestimate the effect of treatments in subsequent years. As no data regarding maintenance of effect of treatment are available, this assumption is highly uncertain. However, CDR was unable to test the impact of the constant transition probability given the structure of the model.

- **The utility value used for the post-transplant health state does not meet face validity:** CDR notes the utility value used for the post-transplant health state does not appear to meet face validity: feedback from the CDR clinical expert indicated that the assumption that patients in the post-transplant health state would have a higher quality of life (utility) score than patients in the mild disease state was unlikely to be accurate. The CDR clinical expert noted that although a transplant may improve lung function, patients who receive a transplant are now immunocompromised and are at increased risk of developing infections, lymphoproliferative disease, and diabetes; and their digestive issues are still present. While there is benefit and patients improve from their quality of life before transplant, the improvement is tempered with other issues. CDR also noted that the base FEV_1 health states were sourced from UK estimates. Since Canadian values could not be identified, there is some uncertainty regarding the generalizability of the values used.
- **Rates of exacerbation are associated with uncertainty, and the definitions of exacerbation are likely to differ in clinical practice compared with the trial and model assumptions:** The manufacturer used exacerbation rates from a post-hoc analysis of the MPEX-209 trial for levofloxacin and tobramycin solution, and applied an odds ratio of the event occurring for aztreonam and tobramycin powder. Feedback from the CDR clinical expert suggested that in practice, the definition of an exacerbation isn't as rigid as the requirements indicated in clinical trials as used in the economic analysis, which may therefore underestimate the overall number of exacerbations reported. However, it is unknown whether this would lead to a difference in exacerbation rate between treatments. Also, uncertainty occurs as the MPEX-209 trial only captured first exacerbation event, and the manufacturer assumed that patients will only experience one exacerbation within the 24-week cycle time, which may be appropriate for patients in mild and perhaps moderate disease, but is less likely to be an appropriate expectation for patients with more severe disease as these patients are likely to experience more exacerbations more frequently. The manufacturer assumed that the risk of major exacerbation was independent of lung function (based on higher FEV_1% predicted), that is, constant for all health states; which is unlikely to be appropriate.
- **Timing of transplantation in the model differs to Canadian clinical practice:** The manufacturer reported that if a patient's FEV_1% predicted value fell below 40, they may undergo transplant. Multiple reports from the patient group Cystic Fibrosis Canada (CF Canada) indicate that individuals may be considered for lung transplantation "if their FEV_1 falls below 30 per cent OR if there is a sudden and rapid decline in FEV_1;"[19,20] thus, the manufacturer may overestimate the number of transplantations. The clinical expert consulted by CDR indicated that while the value noted in the CF Canada reports is accurate in denoting when the process starts (when patients are put on a transplant list); the FEV_1% predicted for most patients' experience, due to wait times, at time of transplant, is approximately 20. CDR was unable to test the impact of this limitation based on the lack of available Canadian data and model structure.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook one-way and multi-way reanalyses based on the limitations identified in the previous section. The CDR best estimate includes revised transition probabilities and exacerbation rates, and a revised health state utility value for the post-transplant health state. This analysis was undertaken comparing levofloxacin with aztreonam, tobramycin powder, and tobramycin solution.

Specifically, for the transition probabilities and exacerbation rates, the CDR best estimate ignored indirect evidence from the NMA and used only direct evidence from the MPEX-209 trial comparing levofloxacin with tobramycin, and assumed equal efficacy for levofloxacin and aztreonam in the absence

of robust evidence indicating otherwise. In addition, the CDR best estimate varied the utility score applied to the post-transplant health state, using instead the utility value that was used for the milder disease health state. The results are reported in Table 4.

TABLE 4: CDR BEST ESTIMATE

Parameter tested	ICUR for Levofloxacin vs. Aztreonam	ICUR for Levofloxacin vs. Tobramycin Powder	ICUR for Levofloxacin vs. Tobramycin Solution
CDR best estimate	No difference in costs or QALYs	$358,486 per QALY	$852,854 per QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

CDR undertook subsequent analyses based on FEV_1% predicted at baseline. The results indicated that levofloxacin was least cost-effective in patients with better FEV_1% predicted at baseline (Table 17).

CDR undertook price reduction scenarios on the comparisons of levofloxacin with tobramycin powder for inhalation and tobramycin solution for inhalation (Table 5). Based on the CDR best estimate, to achieve an ICUR below $50,000 per QALY, the price reduction required for levofloxacin was 22% (versus tobramycin powder) and 57% (versus tobramycin solution).

TABLE 5: CDR REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Levofloxacin versus Tobramycin				
	Versus Tobramycin Powder		Versus Tobramycin Solution	
Price	**Base-Case Analysis Submitted by Manufacturer (adult population)**	**Reanalysis by CDR**	**Base-Case Analysis Submitted by Manufacturer (adult population)**	**Reanalysis by CDR**
$4,045.14	$58,840 per QALY	$358,486 per QALY	$918,269 per QALY	$852,854 per QALY
10 % reduction	$30,011 per QALY	$215,179 per QALY	$763,971 per QALY	$709,547 per QALY
20 % reduction	$8,607 per QALY	$71,872 per QALY	$609,672 per QALY	$566,240 per QALY
25 % reduction	Dominant	$219 per QALY	$532,522 per QALY	$494,587 per QALY
30 % reduction	Dominant	Dominant	$455,373 per QALY	$422,933 per QALY
40 % reduction	Dominant	Dominant	$301,074 per QALY	$279,626 per QALY
50 % reduction	Dominant	Dominant	$146,775 per QALY	$136,320 per QALY
55 % reduction	Dominant	Dominant	$69,626 per QALY	$64,666 per QALY
60 % reduction	Dominant	Dominant	Dominant	Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

6. ISSUES FOR CONSIDERATION

Place in therapy: The Health Canada indication does not preclude the use of levofloxacin as a first-line treatment for adult patients with CF who have *P. aeruginosa* infection. Although the manufacturer has placed levofloxacin as a direct comparator/replacement for aztreonam (post-treatment with tobramycin), feedback from the CDR clinical expert indicates that its place in therapy is difficult to determine. The CDR clinical expert noted that although there are no data indicating which line of therapy levofloxacin fits in, in practice it will likely be used in adults with CF who have chronic pulmonary *P. aeruginosa* infection and in whom tobramycin is not effective at maintaining symptom control and or pulmonary function.

Use in clinical practice: The Health Canada indication limits levofloxacin use to adults 18 years and older, although clinical trials (including the pivotal trial MPEX-209) have been undertaken in patients as young as 12. Although the CDR clinical expert indicated that levofloxacin would likely only be used in adult patients given the Health Canada indication, there is uncertainty regarding its use in patients younger than 18 years old. The product monograph also indicates that the "safety and efficacy of [levofloxacin] have not yet been established beyond three consecutive cycles (six months) of therapy."[1] Feedback from the CDR clinical expert indicated that patients are likely to continue treatment as required beyond the first three cycles.

Sequential use with currently available inhaled treatments: Feedback from the CDR clinical expert noted that levofloxacin is likely to be used sequentially with currently available inhaled treatments. Patients are not often left untreated in the 28-days "off-cycle" that is common with the inhaled treatments for *P. aeruginosa* infection, as physicians are often worried about the infection coming back or patients building up a tolerance to a treatment; thus, another inhaled treatment is often used in that "off-cycle" period, or potentially an intravenous or oral treatment. The manufacturer's economic model doesn't consider or allow for sequential analysis of levofloxacin with other relevant treatments (tobramycin, aztreonam), and this may affect the effect of treatment, and may affect economic considerations and results of the analysis.

Combination use with another inhaled treatment: Feedback from the CDR clinical expert indicated that even though this is not routinely implemented in clinical practice, there is a potential that this actually occurs in practice. This would have a health economic impact, but it could not be assessed.

Comparative adherence of inhaled treatments is uncertain: Feedback from the CDR clinical expert considered that the type of nebulizer used for levofloxacin or comparator treatments may influence compliance. Although clinical experience and familiarity may suggest better adherence with tobramycin, the clinical expert consulted by CDR indicated that the reported reduced time to administer treatment with eFlow nebulizers (such as Zirela) may result in better adherence for levofloxacin than treatments that use other nebulizers. The model assumed 100% adherence and compliance for all treatments, which is likely to be an overestimate given the adherence rates in the trial and other published literature.[21]

7. PATIENT INPUT

Input was received from two patient groups: Cystic Fibrosis Canada (CF Canada) and the Patient Family Advisory Board (PFAB).

The patient input provided information that was mainly generic to the disease (CF), but did provide information regarding treatment of *P. aeruginosa* infections, which is the role that levofloxacin will play.

The two groups reported a lack of experience with levofloxacin, but that patients hope levofloxacin will provide an effective additional treatment option to manage CF symptoms; and reduce exacerbations and infections, thus limiting a need for intravenous antibiotics and hospital admissions, while improving quality of life and preventing or delaying time to lung transplantation. These components were all directly or indirectly considered in the health economic analysis submitted by the manufacturer. Additionally, respondents expressed hope that the drug will be available through a high-efficiency, portable nebulizer.

8. CONCLUSIONS

CDR determined that the relevant comparators for levofloxacin were aztreonam, tobramycin powder, and tobramycin solution for the treatment of *P. aeruginosa* in adult patients with CF. As these comparators could not all be considered simultaneously within a run of the model given the model structure, results compared with levofloxacin were presented separately. CDR attempted to address the key limitations by prioritizing the direct head-to-head evidence, given the uncertainty associated with the NMA submitted by the manufacturer.

Based on the transition probabilities derived from the post-hoc analysis of the MPEX-209 trial and revised utility values and exacerbation rates, the CDR results indicated that levofloxacin is associated with an ICUR of $358,486 per QALY compared with tobramycin powder, and an ICUR of $852,854 per QALY compared with tobramycin solution. Given the uncertainty regarding the comparative clinical efficacy and safety, and the broad product indication, the true cost-effectiveness of levofloxacin and how it could be used in clinical practice is uncertain.

Should levofloxacin and aztreonam be found to be similarly efficacious, levofloxacin is equal in cost to the list price of aztreonam.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Unit prices are from the Ontario Drug Benefit Formulary, unless otherwise specified. Existing Product Listing Agreements are not reflected in Table 6 and as such data in the table may not represent the actual costs to public drug plans.

TABLE 6: CDR COST COMPARISON TABLE FOR DRUGS FOR THE TREATMENT OF *PSEUDOMONAS AERUGINOSA* INFECTION IN PATIENTS WITH CF

Comparators	Strength	Dose Form	Unit Price ($)	Recommended Dose[a]	Daily Drug Cost ($)	Drug Cost per 28 Day Cycle ($)
Levofloxacin (Quinsair)	**240 mg/ 2.4 mL (100 mg/mL)**	**Inhalation solution**	**72.2346[b]**	**240 mg twice daily[c]**	**144.47**	**$4,045.14**
Aztreonam (Cayston)	75 mg	Vial (inhalation)	48.1564	75 mg three times daily[c]	144.47	$4,045.14
Tobramycin (Tobi podhaler)	28 mg	Capsule for inhalation	13.4510[d]	Four capsules twice daily[c]	107.61	$3,013.02
Tobramycin (Tobi, generic)	300 mg / 5mL	Solution for inhalation	27.3815	300 mg twice daily[c]	54.76	$1,533.36
Colistimethate sodium[e] (Colobreathe)	150 mg	Vial for inhalation	33.7397[f]	2.5 mg/kg to 5.0 mg/kg per day[g]	33.74 to 67.48	$944.71 to $1,889.42

CDR = CADTH Common Drug Review; CF = cystic fibrosis.
All prices are from the Ontario Drug Benefit Formulary (accessed August 2016), unless otherwise indicated. Administration fees, dispensing fees, drug delivery system costs, and markups are not included.
[a] Based on respective product monograph.
[b] Current market price as submitted by manufacturer.
[c] Treatment indicates administration as 28 days on treatment, followed by 28 days off treatment.
[d] Saskatchewan Drug formulary (August 2016).
[e] Also known as colistin.
[f] Alberta Drug formulary (August 2016).
[g] A patient weight of 60 kg was assumed.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS LEVOFLOXACIN RELATIVE TO AZTREONAM?[A]

Levofloxacin vs. Aztreonam	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	Equal costs, equal QALYs, equal LYs					

[a] Based on the CDR best estimate.
CE = cost-effectiveness; LY = life-years; NA = not applicable; QALY = quality-adjusted life-years.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS LEVOFLOXACIN RELATIVE TO TOBRAMYCIN SOLUTION FOR INHALATION?[a]

Levofloxacin vs. Aztreonam	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	$852,854 per QALY $6,142,927 per LY					

[a] Based on the CDR best estimate.
CE = cost-effectiveness; LY = life-years; NA = not applicable; QALY = quality-adjusted life-years.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS LEVOFLOXACIN RELATIVE TO TOBRAMYCIN POWDER FOR INHALATION?[a]

Levofloxacin vs. Aztreonam	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	$358,486 per QALY $2,582,100 per LY					

[a] Based on the CDR best estimate.
CE = cost-effectiveness; LY = life-years; NA = not applicable; QALY = quality-adjusted life-years.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 10: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 11: AUTHORS INFORMATION

Authors of the pharmacoeconomic evaluation submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF THE DRUG

The Scottish Medicines Consortium (SMC) recently reported that levofloxacin is accepted for restricted use within NHS Health Scotland after review of a submission under the orphan equivalent process (2016).[22] The economic side of the submission consisted of a cost-minimization analysis (CMA) comparing levofloxacin with aztreonam for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults with cystic fibrosis (the same indication assessed by CADTH Common Drug Review as per the Health Canada one). In the submission to SMC, the manufacturer positioned levofloxacin for third-line use after colistimethate sodium (first line) and tobramycin (second line). Results were presented over three-year, five-year, and lifetime time horizons. The CMA was supported by two network meta-analyses (NMAs) demonstrating the comparative effectiveness of levofloxacin versus aztreonam, which is currently positioned in Scotland after colistimethate sodium and tobramycin. The manufacturer's submission included a patient access scheme. SMC noted that the assumption of comparable efficacy between levofloxacin and aztreonam is uncertain due to the limitations surrounding the NMAs, given the considerable heterogeneity that exists between study populations in relation to previous treatment with inhaled tobramycin. However, the SMC 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, thus, the clinical and economic claims were accepted.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted two base-case economic analyses that compared levofloxacin with aztreonam in patients with cystic fibrosis (CF) who had chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) lung infection.[3] The patient populations for the economic analyses were based on the pivotal study MPEX-209 — a phase III, randomized, open-label, active comparator, non-inferiority trial comparing levofloxacin 240 mg twice daily with tobramycin solution for inhalation 300 mg three times daily in 272 patients 12 years of age and older with CF, who had a forced expiratory volume in one second (FEV_1%) predicted between 25 and 85 and chronic *P. aeruginosa* infection, and who had received at least three 28-day courses (at least 84 days) of inhaled tobramycin solution over the 12 months before screening. Patients were treated for three cycles consisting of 28 days on treatment followed by 28 days off treatment. The trial included patients 12 years and older; approximately 85% of patients were over 18 years of age.[7]

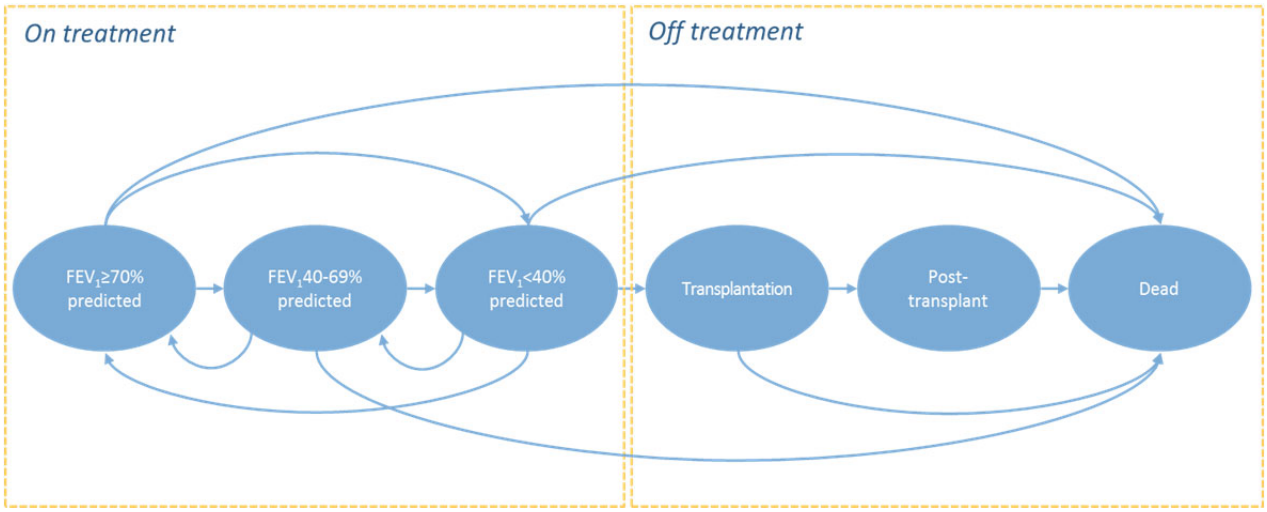
Two cost-utility analyses (CUAs) were submitted that looked at a full patient population (based on the patient population from the MPEX-209 trial – 12 years of age and older), and a subgroup analysis that assessed the results for adult patients (18 year old and older) only, as per the Health Canada indication.[3]

The manufacturer provided two additional CUAs that compared levofloxacin with tobramycin powder for inhalation and with tobramycin solution for inhalation, based on the feedback provided by CADTH at a pre-submission meeting. The manufacturer provided these analyses separately as supplemental analyses, stating that they were not appropriate comparators; thus, were provided for information purposes only. These additional analyses were also reported for the two patient populations assessed by the base case, where the data were available.[3]

The CUAs were developed as a Markov model based on one designed and reported previously by Tappenden et al. in the context of an appraisal by the National Institute for Health and Care Excellence (NICE) in the UK.[4] The CUAs were conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (model ran for 79 years, although 75% are deceased within 18 years [age 48] and 99% of patients are deceased within 35 years [age 65]). The model simulates disease progression of patients with CF who had chronic *P. aeruginosa* infection as determined by a change in lung function, with the potential for lung transplantation and death also considered. FEV_1 % predicted (a comparison of the patient's FEV_1 with the predicted values of healthy patients with similar age, weight, and height) was reported to be a relevant surrogate outcome of change in lung function and thus, used by the manufacturer.[3]

Patients could transition between six health states every 24-weeks (cycle time), which was determined based on the trial length, and the defined treatment course length —4 weeks on treatment, 4 weeks off treatment, repeated three times. The model comprised three FEV_1 health states, a transplant health state, a post-transplant health state, and an absorbing "death" health state (Figure 1).

FIGURE 1: MODEL STRUCTURE



FEV_1 = forced expiration volume in one second.
Source: Manufacturer's Pharmacoeconomic Submission[3]

Patients entered the model in one of the three FEV_1% predicted health states (based on a post-hoc analysis pooling data from both groups of the MPEX-209 trial) and on either treatment with levofloxacin or a comparator. After one treatment cycle, patients could stay in the same FEV_1 state, improve (higher FEV_1) or worsen (lower FEV_1) following transition probabilities. Only patients who are in the lowest FEV_1 state are assumed at risk to undergo transplantation. The model accounted for health-state specific probabilities for exacerbations while in the FEV_1 states. The model assumes there is no relationship between a major exacerbation event and FEV_1 level or treatment. Patients who move out of the FEV_1 health states no longer receive active treatment with levofloxacin, aztreonam, or tobramycin. Mortality rate was affected by age and health state.[3]

A calibration model was developed to estimate posterior distribution of transition probabilities for each treatment analyzed in the economic model, where transition probabilities were predicted using a multinomial logistic regression based on treatment and health state at initiation. The model coefficients were estimated based on the results of the MPEX-209 trial of levofloxacin compared with tobramycin solution for inhalation. As no studies directly compared levofloxacin with aztreonam or tobramycin powder for inhalation, relative efficacy was estimated from a network meta-analysis (NMA) of 24-week studies undertaken by the manufacturer,[6] which was used to determine transition probabilities. Tobramycin solution for inhalation was used as the reference product in the NMA. For the comparison of levofloxacin with tobramycin solution for inhalation, data from the head-to-head trial MPEX-209 were used.[3,7]

Adverse events, aside from exacerbations and the need for transplantation, were not included in the analysis. Transition probabilities for the transplantation and mortality health states were informed by the Tappenden et al. appraisal.[4] The probability of experiencing an exacerbation was based on extrapolating data from the MPEX-209 study and NMA via the Kaplan-Meier method. The probability of experiencing major exacerbation was extracted from the MPEX-209 study and assumed independent of FEV_1 status and current treatment.

TABLE 12: DATA SOURCES

Data Input	Description of Data Source	Comment
Patient characteristics	Background patient characteristics were sourced from MPEX-209 trial (age, distribution of baseline FEV_1% predicted).[3,7]	Feedback from the CDR clinical expert was that this population was generalizable to the Canadian setting, but it was uncertain as to whether the patients included in the study were representative of the patients that would receive treatment.
Efficacy — transition probabilities for disease progression — treatment response	Data from an NMA of 24-week studies were used to inform transition probabilities for FEV_1% predicted for levofloxacin vs. aztreonam and tobramycin powder for inhalation. Tobramycin solution for inhalation was used as the reference product in the 24-week NMA.[6] Data from the MPEX-209 trial were used for transition probabilities for levofloxacin vs. tobramycin solution for inhalation.[3,7]	There is substantial uncertainty associated with the NMA. Individual patient data from the MPEX-209 trial were used to predict probabilities; the precision of the predictions cannot be validated by CDR. NMA results suggest levofloxacin is not significantly different than aztreonam and tobramycin (CDR Clinical Study Report). A published systematic review found no conclusive evidence of a difference in effectiveness between oral anti-pseudomonal treatments.[18] Transition probabilities may appear to fail face validity in some instances. Assumption of constant transition probabilities is unlikely to be appropriate. Other clinical trials of levofloxacin were identified (MPEX-204 and MPEX-207) that were not considered by the manufacturer.
Efficacy — exacerbation rates	Exacerbation per FEV_1 health state due to CF was based on MPEX-209 trial (classified as: 4 of 12 Fuchs symptoms, early discontinuation, death, pulmonary exacerbation as defined by adjudication committee).[3,7] As the MPEX-209 trial only captured the first event, exacerbation probability was estimated using K-M method. Major exacerbation was determined based on the MPEX-209 trial and applied as a constant rate to all FEV_1 health states.	As only first event was captured in MPEX-209, there is uncertainty whether all relevant exacerbations were captured within the 24-week cycle time. Feedback from the CDR clinical expert suggested the Fuchs criteria was rigid and not specifically followed in clinical practice; having 3 of the 12 symptoms may be enough for a physician to note an exacerbation.
Event — transplantation	Probability of undergoing lung transplantation was sourced from Tappenden et al.,[4] which was based on a UK CF registry.	Generalizability of UK data to Canadian practice is uncertain.
Event – mortality	CF patient survival was determined using survival parameters from Tappenden et al.[4] which were	Generalizability of UK data to Canadian practice is uncertain. Model only looks

Data Input	Description of Data Source	Comment
	based on a long-term UK survival study.[23]	at 1 year post-transplant mortality; the CDR clinical expert noted 5-year survival post-transplant was 70%.
Utilities	FEV_1 health state utilities were sourced from a publication that reported the results of an online survey in the UK.[10] Transplant health state utilities were sourced from a published study[24] and were the same as those used in the ivacaftor submission to NICE.[9] Alternative values sourced in a Canadian study were tested in a scenario analysis.[13] Disutility due to exacerbations were sourced from a study of 94 CF patients via the EQ-5D.[11]	Some of the utility values reported appear to fail face validity; feedback from the CDR clinical expert was that assumption of a higher utility for post-transplant than for the best FEV_1 health state was not likely to be appropriate. Generalization of applying UK utility values to the Canadian setting is associated with uncertainty.
Costs		
Levofloxacin	Manufacturer assumed a price per dose that equates to the same cost of a 28-day pack of aztreonam.	The actual cost of aztreonam to drug plans may be lower than the published price, so there is uncertainty as to whether this assumption is accurate and operationalizable.
Comparators	Aztreonam: Ontario EAP formulary TIS: Ontario drug formulary TIP: Alberta drug formulary A maintenance cost for TIS/TIP nebulizer was included based on the UK setting.	Drug cost sources are reasonable. The nebulizer maintenance cost applied to tobramycin is not justified for inclusion in the Canadian setting.
Administration	Cost of nebulizer units for levofloxacin and aztreonam were assumed to be provided by the manufacturer.	Accepted as appropriate.
Health state: CF	CF costs were derived from a Canadian (Ontario) study of administrative health record data.[12] Cost of CF was constant across FEV_1 states.	Generally appropriate.
Event: Transplant	Transplant and post-transplant costs were derived from a Canadian (Quebec) study of lung transplantation that followed patients for 3 years post-transplant.[13]	Cost of transplantation may be conservative.
Event: Exacerbations	Costs for minor exacerbations were based on expert opinion, cost source appears to have been provincial formulary [though not stated] (2 specialist visits and 14 days of oral antibiotics). The cost of a major exacerbation was sourced from CIHI PCE (CMG 432).[14]	Resource use for minor exacerbation seems appropriate. Cost of major exacerbation seems appropriate; potentially conservative based on updated costs available on the PCE (June 2016).

CDR = CADTH Common Drug Review; CF = cystic fibrosis; CIHI = Canadian Institute for Health Information; EAP = Expanded Access Program; EQ-5D = EuroQol 5-Dimensions questionnaire FEV_1 = forced expiration volume in one second; KM = Kaplan-Meier; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PCE = patient cost estimator; TIP = tobramycin powder for inhalation; TIS = tobramycin inhalation solution.

TABLE 13: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
All relevant comparators were included in the base-case analysis.	Not accurate in the Canadian context. Tobramycin (as powder or solution) is an appropriate comparator in a population where levofloxacin is considered in patients that haven't received tobramycin. Manufacturer provided supplemental analyses comparing levofloxacin with TIS/TIP; however, these were provided as separate models. It was not possible for CDR to consider results from sequential analyses.
Lung function is the most appropriate outcome, and differentiating groups based on the FEV_1 proportions used is appropriate.	The CDR clinical expert felt this was appropriate. The FEV_1 health states were reported to correlate to mild, moderate, and severe cases.
The NMA is conducted appropriately and the transition probabilities derived from the NMA accurately reflect the data.	CDR identified several important limitations that make it difficult to conclude a differential in treatment effects between the inhaled antibiotics; homogeneity, transitivity, and consistency have not been clearly and explicitly met or addressed in the NMA. The NMA did not analyze the results in terms of non-inferiority or equivalence, but based on a lack of statistical significance in the comparisons. CDR concluded that there is no clear evidence of a difference in the comparative efficacy and safety of levofloxacin versus other inhaled antibiotics. The transition probabilities calculated based on the NMA differ substantially from those calculated based on the head-to-head trial (MPEX-209).
Probability of experiencing major exacerbation was assumed independent of FEV_1 status and current treatment.	Feedback from the CDR clinical expert indicated that this was generally an appropriate assumption in the context of the health economic analysis; exacerbations are affected by lung function status, but it is only one factor that has an impact on the potential for exacerbation. However, as noted in relation to the assumption below, patients with a lower FEV_1% predicted are likely to be at greater risk for a major exacerbation.
The proportion of patients experiencing major exacerbation represents only a fraction (1.34%) of the patients that experience an exacerbation of any kind. This is applied as a constant rate, regardless of FEV_1 health state.	Feedback from the CDR clinical expert indicated that only a small proportion of patients experience a major exacerbation; however they also indicated that patients with lower lung function scores (< 40% FEV_1 predicted) are likely to be at greater risk for major exacerbation. If the assumption that levofloxacin has a treatment benefit compared with the comparators in patients with severe disease is accepted, this may be a conservative assumption, as a constant exacerbation rate across disease severity likely results in a higher ICUR than differential exacerbation rates.
Patients do not switch treatments	This is unlikely to be accurate, as patients often use another drug in their "off treatment" cycle for one drug. Patients often switch treatments to avoid building up resistance.

Assumption	Comment
100% treatment compliance	Feedback from the CDR clinical expert was that this was unlikely to be representative of clinical practice. In MPEX-209, treatment compliance was less than 90% in ~50% of patients, including ~15% with less than 60% compliance. However, compliance was roughly equivalent in both treatment groups. The impact of revised compliance rates in the model is uncertain, but unlikely to have a substantial impact on the results.
Patients can only experience one exacerbation per cycle.	Feedback from the CDR clinical expert suggests that while in general this may be an appropriate assumption, particularly for patients with mild to moderate illness, patients with worse lung function may have multiple exacerbations over a 24 week period.
Patients who have a FEV_1 < 40% may undergo transplantation.	CF Canada[19,20] indicates that "Individuals may be considered for transplantation if their FEV_1 falls below 30 per cent OR if there is a sudden and rapid decline in FEV_1;" thus, the 40% cut-off may not be the most appropriate cut-off.

CF = cystic fibrosis; CDR = CADTH Common Drug Review; FEV_1 = forced expiration volume in one second; ICUR = incremental cost-effectiveness ratio; NMA = network meta-analysis; TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution.

Manufacturer's Results

As noted earlier, the manufacturer presented two base-case analyses: one compared levofloxacin with aztreonam in all patients included in the MPEX-209 trial (12 years and older), and one compared levofloxacin with aztreonam in a subgroup of patients 18 years or older (in line with the Health Canada–approved indication). CDR focused on the Health Canada–approved indication.

Over the model lifetime time horizon for the Health Canada–approved indicated patient population (18 years and older), patients receiving levofloxacin accrued 0.707 more quality-adjusted life-years (QALYs) compared with patients receiving aztreonam at an incremental cost of $2,193. The resulting incremental cost-utility ratio (ICUR) for levofloxacin was $3,101 per additional QALY gained versus aztreonam. For the full population (included pediatric patients), the ICUR for levofloxacin was $4,061 per additional QALY gained versus aztreonam.[3]

TABLE 14: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASES

	Total Costs	Incremental Cost of Levofloxacin	Total QALYs	Incremental QALYs of Levofloxacin	Incremental Cost per QALY
Subgroup: 18 years or older					
Aztreonam	$298,306		4.896		
Levofloxacin	$300,499	$2,193	5.604	0.707	$3,101
Full population					
Aztreonam	$319,531		5.343		
Levofloxacin	$322,041	$2,510	5.961	0.618	$4,061

QALY = quality-adjusted life-year.
Source: Based on Manufacturer's Pharmacoeconomic Submission.[3]

The manufacturer presented several supplemental analyses based on the two patient populations, with two additional comparators; tobramycin inhalation powder and tobramycin inhalation solution. Analyses that compared levofloxacin with tobramycin inhalation powder were based on the results of the NMA,[6] and the ones that compared levofloxacin with tobramycin inhalation solution were based on data from the head-to-head trial MPEX-209. In the relevant patient population (18 years or older, per the Health Canada indication), the ICUR for levofloxacin compared with tobramycin inhalation powder was $58,840 per QALY; while compared with tobramycin inhalation solution, the ICUR was $918,269 per QALY (Table 15).

TABLE 15: SUMMARY OF RESULTS OF THE MANUFACTURER'S SUPPLEMENTAL ANALYSES

Comparison	Patient Population	Incremental Cost of Levofloxacin	Incremental QALYs of Levofloxacin	Incremental Cost per QALY
Levofloxacin vs. TIP	Subgroup: 18 years+	$51,415	0.874	$58,840
	Full population	$54,246	0.798	$67,966
Levofloxacin vs. TIS	Subgroup: 18 years+	$125,511	0.137	$918,269
	Full population	$133,111	0.131	$1,016,770

QALY = quality-adjusted life-year; TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution.
Source: Based on Manufacturer's Pharmacoeconomic Submission.[3]

The manufacturer undertook a series of one-way deterministic sensitivity analyses, testing most model inputs on the base-case analyses of levofloxacin compared with aztreonam. As noted above, CDR focused on the Health Canada–approved indication. The main drivers of the ICUR were the mortality hazard ratio, CF costs, post-transplant costs, and distribution for FEV_1. The manufacturer undertook a probabilistic sensitivity analysis (PSA) using 2,000 simulations. The results of the PSA indicated that for the population 18 years or older, there was a 99.2% probability that levofloxacin would be cost-effective compared with aztreonam at a willingness to pay of $100,000 per QALY.[3]

The manufacturer undertook additional scenario analyses on their full population base-case analysis using different utility values (Tappenden et al.)[4] for FEV_1 states and for post-transplant states (Vasiliadis et al.),[13] a different extrapolation approach for FEV_1 transition probabilities and exacerbation rates, and lower discount rates. None of these revised scenarios appeared to have much of an impact on the results.

CADTH Common Drug Review Reanalyses

The following limitations led to the CDR reanalyses reported in Table 16:

Not all relevant comparators were considered in the manufacturer's base-case analysis: The manufacturer did not consider tobramycin powder, tobramycin solution, and colistin as relevant comparators for levofloxacin for their base-case analysis. However, feedback from the CDR clinical expert indicated that as inhaled colistin is not recommended in Canada given the low use of colistin in practice, it was appropriate that a comparison was not presented. Hence, CDR considered three analyses of relevance for decision-making, comparing levofloxacin with tobramycin powder, with tobramycin solution and with aztreonam, and performed reanalyses focusing on the Health Canada–approved indication (adult patients).

The validity of the transition probabilities is associated with substantial uncertainty: The manufacturer derived transition probabilities from a manufacturer-sponsored NMA of 24-week studies for the comparisons of levofloxacin with aztreonam and tobramycin powder. CDR identified substantial limitations with the manufacturer's NMA (refer to the CDR Clinical Study Report), which resulted in substantial uncertainty in the results. Additionally, the transition probabilities for levofloxacin based on the 24-week NMA do not align with the transition probabilities for levofloxacin based on the MPEX-209 clinical trial, and appear to overestimate the comparative effect of levofloxacin against aztreonam. Thus, CDR used data from MPEX-209 to inform the levofloxacin inputs. The model also assumes constant transitions over the patient's lifetime, i.e., constant levels of effect, which may be an overestimate of the effect in subsequent years, given the lack of long-term data for levofloxacin in the patient population of interest, hence the lack of evidence for assuming this maintenance of effect. Based on the findings of the CDR clinical review (in which CDR concluded no clear evidence of a difference in the comparative efficacy and safety of levofloxacin versus other inhaled antibiotics) and previously published evidence that suggested that treatment with tobramycin powder was non-inferior to tobramycin solution,[17] CDR used the transition probabilities from the tobramycin solution group of the MPEX-209 trial to inform the transitions for tobramycin powder.

The base-case utility values are associated with uncertainty, and the value used for the post-transplant health state does not meet face validity: Based on a targeted review of the literature CDR notes that no other more appropriate FEV_1 health state values appear to have been published. The post-transplant utility values do not appear to meet face validity: feedback from the CDR clinical expert suggested that the assumption that patients in post-transplant would have a higher quality of life (utility) score than patients with mild disease state was unlikely to be appropriate, as although a transplant may improve lung function, patients who receive a transplant are now immunocompromised and are at increased risk of developing infections, lymphoproliferative disease, and diabetes; and their digestive issues are still present. While there is benefit and patients improve from their quality of life as compared with pre-transplant, the improvement is tempered with other issues. CDR tested a constant revised utility value for the post-transplant health state, assuming equivalent utility score to the milder FEV_1% predicted health state. CDR also noted that the base FEV_1 health states were sourced from UK estimates. While Canadian values could not be identified, there is some uncertainty regarding the generalizability of the values used.

Rates of exacerbation are associated with uncertainty, and definition is likely to differ in clinical practice compared with the trial and model assumptions: The manufacturer's definition of exacerbation for levofloxacin was based on the clinical trial MPEX-209,[7] and data used were derived from a post-hoc analysis of the MPEX-209 trial for levofloxacin and tobramycin solution, and then applied an odds ratio of the event occurring for aztreonam and tobramycin powder. Feedback from the CDR clinical expert suggested that in clinical practice, the definition of an exacerbation is less rigid. Also, uncertainty occurs as the MPEX-209 trial only captured first exacerbation event, and the manufacturer assumed that one exacerbation can occur per 24-week cycle in the model. For severe disease, more than one exacerbation can happen during a 24-week length cycle. Thus, it is uncertain as to the actual proportion of exacerbations that would be experienced by patients in practice and the comparative exacerbation rate between treatments, especially for the comparative rates taken from the NMA for the comparison of levofloxacin versus aztreonam and versus tobramycin powder, considering the uncertainty of the NMA results. Given the information above, available data, and aligning with the CDR assessment of transition probabilities, CDR used the exacerbation rates from the levofloxacin group of the MPEX-209 trial for levofloxacin and for aztreonam, and proportions from the tobramycin solution group in the MPEX-209 trial for both tobramycin solution and tobramycin powder.

TABLE 16: CDR REANALYSES

Parameter Tested	ICUR for Levofloxacin vs. Aztreonam	ICUR for Levofloxacin vs. Tobramycin Powder	ICUR for Levofloxacin vs. Tobramycin Solution
Manufacturer's analyses	$3,101 per QALY	$58,840 per QALY	$918,269 per QALY
Revised transition probabilities	Dominated	$340,935 per QALY	$918,269 per QALY
Revised base-utility values	$2,961 per QALY	$56,237 per QALY	$852,854 per QALY
Revised minor exacerbation rate	$2,387 per QALY	$60,363 per QALY	$918,269 per QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CDR Best Estimate

CDR undertook a reanalysis combining each of the reanalyses presented in Table 16. This combined analysis represents the CDR best estimate (Table 17).

CDR also noted that there is uncertainty as to whether the patient population used to inform the economic model is representative of patients expected to receive levofloxacin in practice. The MPEX-209 trial included patients who had received at least three 28-day courses or a total of 84 days of an inhaled antimicrobial over the previous 12 months, with at least a 14-day course being completed within 29 to 84 days before visit 1 and were clinically stable with no significant changes in health status within the last 28 days before visit 1. Given patients were being treated and were clinically stable, it is uncertain as to why physicians would alter patients' treatment regimen. Due to the uncertainty of the patient population and results, CDR undertook subsequent reanalyses on the CDR best estimate assuming all patients started in each of the different baseline health states in individual analyses (Table 17).

TABLE 17: CDR BEST ESTIMATE

Parameter Tested	ICUR for Levofloxacin vs. Aztreonam	ICUR for Levofloxacin vs. Tobramycin Powder	ICUR for Levofloxacin vs. Tobramycin Solution
CDR best estimate	No difference in costs or QALYs	$358,486 per QALY	$852,854 per QALY
All patients start in $FEV_1 \geq 70\%$	No difference in costs or QALYs	Dominated	Dominated
All patients start in FEV_1 40% to 69%	No difference in costs or QALYs	$246,376 per QALY	$583,835 per QALY
All patients start in $FEV_1 < 40\%$	No difference in costs or QALYs	$332,802 per QALY	$793,617 per QALY

CDR = CADTH Common Drug Review; FEV_1 = forced expiration volume in one second; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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