Common Drug Review
Clinical Pharmacoeconomic Report

April 2017

Drug	Reslizumab (Cinqair)
Indication	Cinqair (reslizumab) is indicated as an add-on maintenance treatment of adult patients with severe eosinophilic asthma who: are inadequately controlled with medium-to-high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA); and have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment.
Reimbursement request	As per indication
Dosage form(s)	10 mg/mL vial, concentrate for solution for intravenous infusion
NOC Date	July 20, 2016
Manufacturer	Teva Canada Innovation

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and clinical immunology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptoms Utility Index
CDR	CADTH Common Drug Review
CI	confidence interval
CMA	cost-minimization analysis
CUA	cost-utility analysis
DDA	day-to-day asthma
DEA	death from asthma
DOC	death from other causes
EAE	emergency room visit for asthma exacerbation
FEV_1	forced expiratory volume in one second
HAE	hospitalization for asthma exacerbation
ICS	inhaled corticosteroid
ICUR	incremental cost-utility ratio
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
MCID	minimal clinically important difference
NAE	unscheduled general physician visit for asthma exacerbation
NMA	network meta-analysis
OAE	oral corticosteroid for asthma exacerbation
OCS	oral corticosteroid
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SOC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Reslizumab (Cinqair)
Study Question	The objective of this study was to perform a CUA of reslizumab (in addition to SOC) compared with SOC for the treatment of inadequately controlled severe eosinophilic asthma in Canada. In addition, a CMA was completed to compare reslizumab with mepolizumab and omalizumab.
Type of Economic Evaluation	Primary analysis: CUA Secondary (supplemental) analysis: CMA
Target Population	Adult patients (at least 18 years of age) with inadequately controlled severe eosinophilic asthma who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) (e.g., LABA) and have a blood eosinophil count of ≥ 400 cells/μL at initiation of treatment
Treatment	Reslizumab 3 mg/kg via intravenous infusion every 4 weeks in addition to SOC
Outcome	QALYs
Comparators	Primary analysis: SOC alone Secondary analysis: mepolizumab, omalizumab
Perspective	Provincial Ministry of Health perspective
Time Horizon	Lifetime (approximately 50 years)
Results for Base Case	Reslizumab + SOC vs. SOC alone: • ICUR = $256,090 per QALY Reslizumab vs. mepolizumab and omalizumab: • Reslizumab is cost-saving ($2,174 to $3,107 per year)
Key Limitations	Key limitations of the CUA: • Duration of reslizumab use (10 years) is uncertain, and a substantial proportion of QALY benefits of reslizumab were found to accrue after treatment discontinuation as a result of an assumed survival benefit with reslizumab that is not supported by the clinical data. • Utility values were derived from a source of uncertain validity, and the application of utility values was not appropriate and not supported by the trial data for one of the key health states in the model. • Not all relevant comparators were considered. Other treatments, particularly LAMAs, should have been included as direct comparators for reslizumab, as they are options for patients with inadequate asthma control with ICS plus LABA. • Definition of response may not reflect Canadian practice, and patients in clinical practice likely receive treatment for longer than the initial treatment period in the model (16 weeks) before determining response. • There is uncertainty regarding the real-world distribution of patient body weights, which in turn reduces the certainty for estimates of the average annual cost of reslizumab. The clinical expert consulted by CDR indicated that the weight distribution used in the manufacturer's base case may have been underestimated, potentially biasing cost-effectiveness results in favour of reslizumab. (This limitation is also applicable to the CMA.) Key limitations of the CMA: • Uncertain comparative effectiveness as a result of limitations of manufacturer-submitted indirect comparison, particularly of reslizumab vs. omalizumab • Number of vials of omalizumab per patient per month may have been overestimated, potentially biasing results in favour of reslizumab, although CDR noted uncertainty in the vial calculation and the potential for jurisdictional differences

	• Wholesale price of mepolizumab was used in the analysis, as it was the only publicly available price, which may overestimate the cost of treatment, given that CDR has recommended that mepolizumab be listed with a substantial price reduction
CDR Base Case	The CDR base case ICUR for the deterministic analysis of reslizumab + SOC compared with SOC alone was $888,000 per QALY. Based on the probabilistic analysis, the ICUR was approximately $1.2 million per QALY. A price reduction of 95% or 89% would be required for reslizumab + SOC to be cost-effective, based on thresholds of $50,000 per QALY and $100,000 per QALY, respectively. The revised CMA undertaken by CDR indicated that reslizumab was associated with higher annual costs than omalizumab when omalizumab-treated patients received less than 2.83 vials per 28-day period. Reslizumab was found to be less costly than mepolizumab based on the wholesale price. However, the cost comparisons between reslizumab and mepolizumab or omalizumab will ultimately depend on the effective costs to drug plans for the latter two therapies (where listed), and on average utilization of omalizumab.

CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CUA = cost-utility analysis; ICS = inhaled corticosteroids; ICUR = incremental cost-utility ratio; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

EXECUTIVE SUMMARY

Background

Reslizumab (Cinqair) is a selective immunoglobulin G (IgG)4 kappa humanized monoclonal antibody that targets and binds specifically to interleukin-5, and interferes with interleukin-5 binding to its cell-surface receptor. It is available as a 10 mg/mL vial of concentrate for solution for intravenous infusion, and has received Health Canada approval as add-on maintenance treatment to standard of care (SOC) for adult patients with severe eosinophilic asthma that is inadequately controlled with medium- to high-dose inhaled corticosteroids (ICS) and at least one additional asthma controller (e.g., long-acting beta-agonist [LABA]), and have a blood eosinophil count of ≥ 400 cells/µL at initiation of treatment.[1-3] Treatments used as part of SOC were based on asthma-related medications received by patients in the placebo group of the two pivotal reslizumab clinical trials (Study 3082 and Study 3083), which included LABAs, oral corticosteroids (OCSs), and leukotriene receptor antagonists at a constant dosage.[2] The manufacturer submitted reslizumab at a unit price of $640.00 per vial.[1]

The manufacturer's primary economic evaluation was a cost-utility analysis (CUA) comparing reslizumab plus SOC with SOC alone in the population covered by the Health Canada–approved indication. The model incorporated an initial decision-tree approach that considered treatment response with a subsequent Markov model with health states representing day-to-day asthma, asthma exacerbations, and death. If patients responded to reslizumab at the end of the initial 16 weeks of treatment, they were assumed to continue treatment for 10 years before switching to SOC alone for the duration of the model (lifetime, assumed 50 years in total). The manufacturer's deterministic analysis reported an incremental cost-utility ratio (ICUR) of approximately $256,000 per quality-adjusted life-year (QALY). The manufacturer also undertook a probabilistic sensitivity analysis (PSA) using 1,000 simulations, which found a 0% probability that reslizumab would be cost-effective at a threshold of $100,000 per QALY.[2]

The manufacturer also undertook a supplemental cost-minimization analysis (CMA) of reslizumab compared with the other biologics, based on a manufacturer-funded network meta-analysis (NMA), which reported that reslizumab is comparable in efficacy to mepolizumab and omalizumab.[4] The manufacturer's CMA indicated the annual drug cost of reslizumab was less than that of mepolizumab and omalizumab.[2]

Summary of Key Limitations

The CADTH Common Drug Review (CDR) noted several key limitations of and sources of uncertainty in the manufacturer's economic evaluation:

- The model indicated a substantial incremental benefit with reslizumab in the post-reslizumab treatment period, based primarily on an assumption of improved survival, which is not warranted based on the available clinical data.
- The manufacturer applied different utility values based on treatment within a single health state, which is not appropriate. As well, as the values were from an asthma-specific utility scale that is of uncertain validity as a source of health-state utilities.
- Clinical data on exacerbations used to inform the model were based on a mixture of unpublished, post hoc, pooled subgroup analyses that could not be fully validated by CDR.
- The definition of response to initial treatment used in the model may not reflect Canadian clinical practice; in particular, the forced expiratory volume in one second (FEV_1) threshold for defining response in practice is twice that used in the model, according to the clinical expert consulted by

CDR. Furthermore, biologic therapy may be tried for six months, rather than 16 weeks as in the model, before determining response.
- The manufacturer's model did not consider long-acting muscarinic antagonists (LAMAs) as a relevant comparator. LAMAs are currently used in practice in patients who do not respond to an ICS + LABA strategy, and are recommended for such use in clinical practice guidelines.[5]
- The asthma mortality rate may have been overestimated in the model.

The main limitations associated with the manufacturer's CMA of reslizumab versus mepolizumab and omalizumab were as follows:
- Because of substantial heterogeneity and other limitations of the manufacturer's submitted NMA, CDR could not form any conclusions regarding the comparative efficacy of reslizumab and omalizumab; therefore, the appropriateness of a cost comparison, rather than cost-effectiveness analysis, of these two drugs is uncertain.
- The manufacturer may have overestimated the real-world average number of vials per 28-day cycle of omalizumab, potentially biasing the results of the CMA in favour of reslizumab. While CDR independently estimated average vials per claim using utilization data, there was uncertainty as to whether this reflected use per 28 days due to the lack of information on the number of days' supply and the variable administration schedule for the drug (i.e., every two or four weeks).
- Mepolizumab is not currently listed by any public drug plans in Canada; therefore, the manufacturer used the wholesale price in the CMA. Alternative price scenarios for mepolizumab were not considered.
- According to the clinical expert consulted by CDR, the distribution of patient body weights used to estimate average reslizumab doses and costs may have been underestimated in both the CUA and CMA, potentially biasing results in favour of reslizumab. There were no reliable data to inform patient weight distribution; therefore, CDR considered that the real-world average cost of reslizumab was uncertain. CDR noted that slight alterations to the weight distribution affected the annual cost of reslizumab compared with mepolizumab and omalizumab, although cost-effectiveness estimates versus SOC were minimally affected. Patient weight distributions may differ between jurisdictions and should be taken into account when considering comparative costs.

Key Results and Conclusions

CDR undertook several one-way deterministic sensitivity analyses to test revised assumptions to address the identified limitations of the CUA, when possible, as well as a multi-way analysis combining several of the revised assumptions (the time horizon was reduced to be equal to the duration of reslizumab treatment; utility values were revised and made consistent for each health state regardless of treatment; a lower asthma mortality rate was used; the cost of SOC was assumed to be same for both treatment arms; and the weight distribution was revised, which slightly increased the annual cost of reslizumab). The CDR deterministic base case for reslizumab + SOC compared with SOC alone in adults with severe eosinophilic asthma was approximately $888,000 per QALY, and the mean probabilistic ICUR (based on 5,000 simulations) was approximately $1.2 million per QALY. Based on CDR's base case, a price reduction of 95% would be required for the ICUR of reslizumab + SOC compared with SOC alone to fall below $50,000 per QALY in adults with severe eosinophilic asthma, while an 89% price reduction would be required to achieve an ICUR of $100,000 per QALY.

CDR reviewers were unable to validate the conclusion of the manufacturer's indirect comparison that these drugs have similar efficacy; therefore, the use of a CMA to compare them may not have been appropriate. CDR reanalyses of the CMA indicated that alternative assumptions regarding the

distribution of patient weights and omalizumab use affected the comparative cost analysis. Reslizumab is more costly than omalizumab when patients receive fewer than 2.83 vials of omalizumab per 28 days, and less costly than mepolizumab based on wholesale prices. However, the cost comparison between reslizumab and mepolizumab or omalizumab in a given jurisdiction will ultimately depend on the effective costs for the latter therapies, patient weight distribution, and average omalizumab dose. Based on the available clinical evidence, CDR considered that there was no justification for a price premium for reslizumab over either omalizumab or mepolizumab.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer's primary economic analysis was a cost-utility analysis of reslizumab as an add-on to standard of care (SOC) compared with SOC alone in adults with severe eosinophilic asthma inadequately controlled with an inhaled corticosteroid (ICS) and another asthma medication. Treatments used as part of SOC were based on asthma-related medications received by patients in the placebo groups of Study 3082 and Study 3083, which included long-acting beta-agonists (LABAs), oral corticosteroids (OCSs), and leukotriene receptor antagonists at a constant dose. The analysis was undertaken from the perspective of a ministry of health in Canada over a lifetime time horizon (approximately 50 years) with all costs and outcomes discounted at a rate of 5% annually.[2]

The model population characteristics were derived from a subgroup of patients from the pivotal clinical trials of reslizumab (Study 3082 and Study 3083) that were aligned with the Health Canada–approved indication. The cost-utility analysis was developed using a decision-tree approach over the initial 16 weeks (Figure 1) to assess clinical response based on an unpublished post hoc, pooled, subgroup analysis of Study 3082 and Study 3083.[2] Response was defined as an improvement in forced expiratory volume in one second (FEV_1) of ≥ 0.1 L from baseline; such an improvement was reported in 57% of patients receiving reslizumab. Patients who responded to reslizumab based on pooled data from Studies 3082 and 3083 were assumed to continue treatment for an additional 10 years before switching to SOC.[2] Non-responders switched to SOC after the 16 weeks of treatment.

After the initial 16-week treatment period, patients transitioned every two weeks between seven Markov health states consisting of a day-to-day asthma state, exacerbation events, and death (Table 12, Figure 2). All patients entered the Markov model in a baseline health state representing day-to-day asthma; patients in this state were assumed to have a higher utility if treated with reslizumab + SOC compared with patients treated with SOC alone. The probability of patients transitioning between health states was based on exacerbation rates reported in Castro et al.[6] (which reported both separate and pooled results for Studies 3082 and 3083) and the clinical study reports of Studies 3082 and 3083.[2,7,8] However, additional post hoc analyses were undertaken to obtain adjusted values that were used in the economic model. These inputs were subject to some uncertainty, as the underlying methods and subgroups analyzed were not published or described in detail.

Utility values for the day-to-day asthma health states were derived from the Asthma Symptom Utility Index (ASUI) administered in Study 3082 and Study 3083, while utility values for other health states were determined from published literature.[9,10] Drug costs were provided by the manufacturer or sourced from the Ontario Drug Benefit Formulary.[11] Event and health-state costs were obtained from a variety of published Canadian sources.[2,12-14]

The manufacturer also undertook a secondary cost-minimization analysis (CMA) to assess the comparative acquisition costs of reslizumab, mepolizumab, and omalizumab, based on the results of a manufacturer-sponsored network meta-analysis (NMA), which reported that reslizumab was comparable to mepolizumab and omalizumab in terms of efficacy and safety.[4] The manufacturer's CMA included several assumptions regarding patient weight, treatment utilization, and drug costs.

2. MANUFACTURER'S BASE CASE

The manufacturer reported in its base-case deterministic analysis that the incremental cost-utility ratio (ICUR) for reslizumab in addition to SOC compared with SOC alone was $256,090 per quality-adjusted life-year (QALY; Table 2). The mean ICUR from the manufacturer's probabilistic analysis was higher ($304,167 per QALY).

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

	Total Costs	Incremental Cost of Reslizumab	Total QALYs	Incremental QALYs of Reslizumab	Incremental Cost per QALY
Deterministic results					
SOC	$32,650		4.005		
Reslizumab + SOC	$139,058	$106,407	4.421	0.4155	$256,090
Probabilistic results (1,000 simulations)					
SOC	$31,699		4.243		
Reslizumab + SOC	$142,338	$110,639	4.606	0.3637	$304,167

QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

The manufacturer undertook four scenario analyses for reslizumab + SOC compared with SOC alone based on:

- the full trial population including children ($295,000 per QALY)
- patients with two or more exacerbations in the year before treatment ($203,000 per QALY)
- a single day-to-day utility value for both treatments ($331,000 per QALY)
- a shortened treatment duration of five years ($189,000 per QALY).

The manufacturer also undertook an analysis of the drug-acquisition costs of reslizumab compared with mepolizumab and omalizumab, based on several assumptions regarding cost, dosage, and utilization. The results indicated that reslizumab ($23,096) is associated with annual cost savings compared with mepolizumab ($2,174) and omalizumab ($3,107) (Table 18).

Summary of Manufacturer's Sensitivity Analyses

The manufacturer undertook a series of one-way deterministic sensitivity analyses by varying efficacy and utility values using the 95% confidence intervals (CIs), and by varying cost inputs by 25%. These analyses indicated that the model was sensitive to changes in exacerbation rates for placebo and reslizumab (ICUR ranges from $186,000 per QALY to $370,000 per QALY when varied to their 95% CI upper and lower bounds), cost of reslizumab (ICUR ranges from $193,000 per QALY to $352,000 per QALY when the price is decreased or increased by 25%), and discount rate (ICUR = $196,000 per QALY when the discount rate is set at 0%).

The manufacturer undertook a probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation of 1,000 patients. The probabilistic analysis indicated a mean ICUR of approximately $304,000 per QALY (incorrectly reported as $561,000 in the manufacturer's report), with a 0% probability that reslizumab was cost-effective at a threshold of $100,000 per QALY, increasing to a 50% probability that it was cost-effective at a threshold of $300,000 per QALY (Figure 4).

The CADTH Common Drug Review (CDR) undertook reanalyses of the manufacturer's PSA, increasing the number of simulations to 5,000 to achieve greater stability in the model. CDR noted that the mean ICUR remained stable (at approximately $293,000 per QALY), as did the probability of reslizumab being cost-effective at the reported thresholds.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified the following key limitations of and sources of uncertainty in the manufacturer's cost-utility analysis:

- **Duration of reslizumab use is uncertain.** There are limited data regarding the long-term use of reslizumab; thus, the assumption that it will be used continuously for 10 years is associated with substantial uncertainty. Feedback from the clinical expert suggested that, in the absence of other relevant treatments and given the chronic nature of the disease, a 10-year period may underestimate the expected duration of therapy (unless other treatments become available in the future). Additionally, CDR noted that a substantial portion of the incremental benefit in QALYs associated with reslizumab in the model was accrued after treatment discontinuation, mainly resulting from an assumed survival benefit with reslizumab. This assumption was considered inappropriate, as a survival benefit was not found in the reslizumab studies. To account for this, CDR undertook analyses that revised the time horizon such that it was aligned with the duration of treatment, thereby minimizing the impact of the assumed survival benefit on the results.
- **Utility values were associated with uncertainty and misapplied.** The manufacturer used higher utility values for patients receiving reslizumab in the day-to-day asthma state than for patients receiving SOC in the same heath state. This is not appropriate, as it is not representative of the quality-of-life data from the pivotal clinical trials, in which the minimal clinically important difference (MCID) was not achieved for the Asthma Quality of Life Questionnaire (AQLQ), the Asthma Control Questionnaire 7 (ACQ-7), or the Asthma Symptoms Utility Index (ASUI). Additionally, the manufacturer's base health-state values were derived from a questionnaire (ASUI) that has not been validated as an appropriate source of utilities. CDR undertook reanalyses using published utility values for the day-to-day asthma state.
- **There is uncertainty associated with the validity of the efficacy data and model structure.** The manufacturer used a 16-week time period to determine whether patients responded to treatment based on internally derived response criteria and post hoc, pooled, subgroup data from the pivotal reslizumab clinical trials. Feedback from the clinical expert consulted by CDR indicated that the FEV_1 criterion in the response definition is lower than what is considered the MCID in practice (0.23 L, which is also reported in the literature),[15] and the response criterion used in the model may not reflect clinical practice. The expert also indicated that most patients currently receive biologics for six months before determining whether to continue treatment, which suggests that, in practice, response may be measured at a later time point. Additionally, the transition probabilities reflecting response rates at 16 weeks and exacerbation rates throughout the model are based on post hoc subgroup data that CDR was unable to verify, and no reliable alternative values were available to test the effect of these probabilities. Although CDR was able to revise the response rate at 16 weeks, it was unable to extend the initial duration of treatment, as this would have required substantial revisions to model structure that were beyond the scope of the CDR evaluation. An extended initial duration is expected to add a larger incremental cost for the reslizumab arm; however, because the impact on total QALYs cannot be predicted, it is uncertain how a longer initial treatment period would affect the ICUR.
    - **The asthma mortality rate may not be generalizable to the Canadian setting.** CDR noted that the asthma mortality rate was derived from two studies in the UK that appeared to indicate

that the asthma mortality rate was below 1%; yet the manufacturer's calculation resulted in a mortality rate of 1.44%. Feedback from the expert consulted by CDR indicated that Canadian data (albeit somewhat dated) suggested that 20 children and 500 adults die from asthma every year;[16] thus, the assumed rate of 1.44% is likely an overestimate. The manufacturer also assumed in the analysis that the mortality rate was the same regardless of health state, which may not be appropriate but is likely a conservative assumption. CDR tested an asthma mortality rate of 1% per year.

- **The model did not consider relevant comparators.** Feedback from the CDR clinical expert indicated that treatments such as long-acting muscarinic antagonists (LAMAs) should have been included as direct comparators for reslizumab, based on the indication (after failure of ICS + LABA). CDR was unable to undertake a comparison assessing the cost-effectiveness of reslizumab compared with LAMAs because of the lack of comparative clinical information and the model structure. In the absence of comparative clinical data, CDR undertook an exploratory analysis under the most optimistic scenario for reslizumab in which it was assumed that all SOC-alone patients received a LAMA in addition to their current treatment (thereby incurring the cost of the LAMA), but accrued no additional benefit compared with SOC alone. The ICUR for reslizumab did not change appreciably from the base case, indicating that reslizumab is unlikely to be cost-effective compared with addition of a LAMA to ICS + LABA (Table 22).
- **Cost calculation for SOC was underestimated.** The manufacturer underestimated the cost of SOC in the SOC arm compared with the reslizumab arm. CDR revised the SOC costs so that they were the same in both treatment arms.
- **Patient weight distribution is associated with uncertainty.** The source of the patient weight distribution used by the manufacturer was uncertain, and it was also unclear whether the distribution is generalizable to the Canadian setting. Feedback from the clinical expert consulted by CDR indicated that the weight distribution used may underestimate the distribution in Canadian practice. CDR therefore considered the effect of using a revised weight distribution, while noting that weight distributions are likely to differ between jurisdictions. Due to the uncertainty regarding patient weight distribution, the real-world average cost of reslizumab is uncertain.

CDR identified the following key limitations with the manufacturer's CMA:

- The CDR clinical review identified substantial heterogeneity and other limitations with the manufacturer's submitted NMA. Based on these limitations, CDR could not form any conclusions regarding the comparative efficacy of reslizumab and omalizumab. Therefore, the appropriateness of a cost comparison, rather than cost-effectiveness analysis, of these two drugs is uncertain. CDR considered that the evidence from the NMA suggests no substantial differences between reslizumab and mepolizumab 100 mg in terms of efficacy (see CDR Clinical Review Report).
- The manufacturer's assumption of [redacted] vials per 28-day cycle of omalizumab may be an overestimate, based on a CDR review of QuintilesIMS data, which indicated an average of 2.32 to 2.35 vials per claim.[17] Feedback from the clinical expert consulted by CDR noted that most patients in the expert's clinic received two vials every 28 days, which aligns with CDR's estimate based on QuintilesIMS data. However, there is some uncertainty regarding the average number of days' supply reflected in the utilization data, with the manufacturer contending that the QuintilesIMS estimate of 2.32 to 2.35 vials per claim is per 20 days on average.[18] The average utilization of omalizumab may also differ between jurisdictions.
- Mepolizumab is not currently reimbursed by any public drug plans in Canada; therefore, the wholesale price is currently the only publicly available price and was used in the manufacturer's CMA. However, the CADTH Canadian Drug Expert Committee recommended that mepolizumab be

reimbursed on the condition of a substantial reduction in price (reductions of 80% and 89% from the confidential price were required for it to be cost-effective at an ICUR of $100,000 and $50,000 per QALY, respectively).[19] Therefore, alternative price scenarios for mepolizumab could have been modelled in the CMA.

4. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook several reanalyses to address the limitations described in the previous section, when parameters could be reasonably revised in the submitted economic model and cost comparison. The CDR base case incorporated the following revisions:

- The duration and time horizon were set to the same length (10 years).
- The DDA utility values were based on Lloyd et al.[10] and were the same for both treatments.
- The asthma mortality rate was revised to 1%.
- The cost of SOC was assumed to be the same in both the reslizumab + SOC and SOC treatment groups.
- The distribution of patient weights was revised per Table 19.
- The PSA was performed using 5,000 simulations.

Based on these changes, the CDR base-case deterministic ICUR was $888,000 per QALY, and the probabilistic ICUR was approximately $1.2 million per QALY (Table 21). Based on the CDR base case, a price reduction of at least 95% is required for reslizumab + SOC to be considered cost-effective at a threshold of $50,000 per QALY compared with SOC alone, and an 89% reduction is required to achieve an ICUR of $100,000 per QALY (Table 3).

TABLE 3: CDR REANALYSIS PRICE-REDUCTION SCENARIOS (COST-UTILITY ANALYSIS)

ICUR of Reslizumab + SOC Versus SOC Alone		
Price Per Vial of Reslizumab	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted ($640.00)	$256,090 per QALY	$888,657 per QALY
10% reduction ($576.00)	$230,999 per QALY	$799,918 per QALY
20% reduction ($512.00)	$205,897 per QALY	$711,179 per QALY
30% reduction ($448.00)	$180,796 per QALY	$622,440 per QALY
40% reduction ($384.00)	$155,705 per QALY	$533,738 per QALY
50% reduction ($320.00)	$130,603 per QALY	$444,999 per QALY
60% reduction ($256.00)	$105,513 per QALY	$356,260 per QALY
70% reduction ($192.00)	$80,411 per QALY	$267,558 per QALY
80% reduction ($128.00)	$55,320 per QALY	$178,819 per QALY
90% reduction ($64.00)	$30,219 per QALY	$90,080 per QALY
99% reduction ($6.40)	$7,627 per QALY	$10,223 per QALY

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

CDR also revised the manufacturer's CMA comparing reslizumab with mepolizumab and omalizumab. CDR considered a revised patient weight distribution (based on feedback from the clinical expert consulted by CDR) to estimate the annual cost of reslizumab (Table 19) and a revised annual cost of omalizumab based on a lower observed utilization rate (2.35 vials per 28 days) than that used in the manufacturer's analysis (Table 4). These reanalyses indicated that reslizumab was associated with an incremental annual cost compared with omalizumab ($4,655). Thus, a price reduction of nearly 20% was

required for reslizumab to achieve cost parity with omalizumab (Table 4). CDR noted that omalizumab is less costly than reslizumab at the submitted price, as long as the average use of omalizumab is 2.83 vials or less per 28-day cycle.

Similar to the manufacturer's base-case analysis, reslizumab was cost-saving compared with mepolizumab, based on the wholesale price of mepolizumab. As the CADTH Canadian Drug Expert Committee recommended that mepolizumab be reimbursed with a substantial price reduction, the reslizumab price required to achieve cost parity or cost savings versus mepolizumab will depend on the price at which mepolizumab is funded by drug plans (see Table 23 for further analyses with lower mepolizumab prices).

TABLE 4: CDR REANALYSIS OF COST-MINIMIZATION ANALYSIS AND PRICE-REDUCTION SCENARIOS

Price per Vial of Reslizumab	Annual Incremental Cost (Saving) Associated With Reslizumab			
	Versus Mepolizumab		Versus Omalizumab	
	Manufacturer's Base-Case Analysis	CDR Reanalysis	Manufacturer's Base-Case Analysis	CDR Reanalysis
Submitted ($640.00)	($2,174)	($1,491)	($3,107)	$4,655
10% reduction ($576.00)	($4,482)	($3,869)	($5,415)	$2,277
20% reduction ($512.00)	($6,792)	($6,247)	($7,725)	($100)
30% reduction ($448.00)	($9,102)	($8,625)	($10,035)	($2,479)

CDR = CADTH Common Drug Review.

5. ISSUES FOR CONSIDERATION

CDR, in consultation with the clinical expert, noted the following issues for consideration:

- Not all centres in Canada can perform sputum eosinophil cell counts; thus, the requirement for eosinophil counts may be a barrier to prescribing reslizumab.
- As of October 1, 2016, only two provinces have reimbursed omalizumab for severe allergic asthma, and no provinces have reimbursed mepolizumab for severe eosinophilic asthma. The assessments of comparative pricing in this report should be considered in light of any current or future negotiated prices for omalizumab and mepolizumab.
- The manufacturer indicated that it will fund all administration costs associated with reslizumab, including a specialist nurse to monitor for anaphylaxis. Therefore, the only cost to the public payer (beyond the cost of medications) would be for a respiratory medicine specialist visit at week 16 for assessment of response. If, in future, the manufacturer does not fund administration and/or nurse monitoring, or additional monitoring is required, additional costs that have not been accounted for in the CDR reanalyses would be incurred by payers, potentially reducing the cost-effectiveness of reslizumab.

6. PATIENT INPUT

Input was received from two patient groups: the Asthma Society of Canada/National Asthma Patient Alliance and the British Columbia Lung Groups. The patient groups reported that severe asthma affects patients' abilities to pursue physical activity as well as to perform well at work or school, restricts social interactions, and necessitates increased emergency room (ER) visits and hospitalization. Patient groups noted that current treatments are associated with significant limitations for patients with severe asthma, and that there is unmet clinical need for this group. They expect reslizumab will improve

asthma control (lung function), increase the ability to perform leisure (sport) or general everyday activities (e.g., walking, work, sleeping), and lead to reduced or no ER visits or hospital admissions. The submitted economic model assessed many of the clinical outcomes cited by patient groups, including exacerbations requiring hospitalization and ER visits. As well, some assumptions regarding the societal impacts (in terms of costs) were considered in a supplemental analysis conducted from the societal perspective that took into account productivity costs. However, the results were similar for both the public-payer and societal perspectives.

Patient groups reported that individuals with asthma did not appear to use their medications as directed. The submitted model assumed treatment compliance based on clinical trials, which may overestimate the costs and benefits of treatment, as compliance is likely to be higher in trials than in clinical practice. Patients also expressed concern regarding side effects associated with OCS use for exacerbations. The model did consider OCS use as a treatment for exacerbations, but there was no attempt to model the potential reduction in need for OCS with reslizumab treatment and the consequent reduction in OCS-related adverse effects.

7. CONCLUSIONS

Based on CDR reanalyses to address, when possible, the identified limitations of the manufacturer-submitted model, the CDR deterministic base case ICUR for reslizumab + SOC compared with SOC alone in adults with severe eosinophilic asthma was $888,000 per QALY. The mean ICUR from the probabilistic analysis was even higher (approximately $1.2 million per QALY). A price reduction of 95% would be required for the ICUR of reslizumab + SOC compared with SOC alone to fall below $50,000 per QALY, and a reduction of 89% would be required to achieve an ICUR below $100,000 per QALY.

CDR reviewers were unable to validate the conclusion of the manufacturer's indirect comparison that these drugs have similar efficacy; therefore, the use of a CMA to compare them may not have been appropriate. CDR reanalyses of the CMA indicated that assumptions regarding the distribution of patient weights and average omalizumab use affected the comparative cost analysis. Reslizumab is more costly than omalizumab when patients receive fewer than 2.83 vials of omalizumab per 28 days, although this threshold may vary by jurisdiction, depending on the effective unit cost of omalizumab and patient weight distribution. Reslizumab appears to be less costly than mepolizumab, based on the wholesale price. However, the cost comparison between reslizumab and mepolizumab in a given jurisdiction will ultimately depend on the effective cost of mepolizumab to drug plans, should it be reimbursed, and patient weight distribution. Based on the available clinical evidence, CDR considered that there was no justification for a price premium for reslizumab over either omalizumab or mepolizumab.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 5 have been deemed appropriate by the clinical expert consulted by CDR. Costs are manufacturer's list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table, and, as a result, costs may not represent the actual costs to public drug plans.

TABLE 5: CDR COST-COMPARISON TABLE FOR TREATMENTS FOR SEVERE EOSINOPHILIC ASTHMA

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Dosage	Daily Drug Cost ($)	Annual Cost ($)
Reslizumab (Cinqair)	**10 mg/mL**	**Vial of solution for IV infusion**	**640.00[a]**	**640.00 to 2,560.00[b]**	**3 mg/kg every 4 weeks**	**22.86 to 91.43**	**8,349 to 33,394**
Mepolizumab (Nucala)	100 mg/mL	Vial of powder for SC injection	1,938.46[c,d]	1,938.46	100 mg every 4 weeks	69.23	25,286
Other biologics indicated for a similar population							
Omalizumab (Xolair)	150 mg	Vial (sterile powder for reconstitution) for SC injection	624.24[e]	624.24 to 1,872.72	150 to 375 mg every 2 or 4 weeks[f]	Lowest dose: 22.29 Highest dose: 133.77	Lowest dose: 8,143 Highest dose: 48,858

CDR = CADTH Common Drug Review; IgE = immunoglobulin E; SC = subcutaneous.
[a] Manufacturer's submitted price.
[b] Assumed weight range 30 kg to 120 kg.
[c] Mepolizumab was submitted to CDR at a confidential price in November 2015.
[d] Delta PA, manufacturer's list price, accessed October 2016.[20]
[e] Ontario Drug Benefit Exceptional Access Program (accessed October 18, 2016).[21]
[f] Dose depends on body weight and baseline IgE — can range from 150 mg to 300 mg when administered every 4 weeks, and 225 mg to 375 mg when administered every 2 weeks.[22]

TABLE 6: COST-COMPARISON TABLE FOR OTHER TREATMENTS FOR PATIENTS WITH ASTHMA

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
ICS							
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	MDI (120 doses)	23.9300 41.2800 82.5400	0.1994 0.3440 0.6878	100 mcg 250 mcg 500 mcg twice daily	0.80 to 2.75	291 to 1,005

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Fluticasone propionate (Flovent Diskus)	100 mcg 250 mcg 500 mcg	Inhalant powder (60 doses)	23.9300[a] 41.2800 64.2000	0.3988 0.6880 1.0700	100 mcg 250 mcg 500 mcg twice daily	0.80 to 2.14	291 to 782
Ciclesonide (Alvesco)	100 mcg 200 mcg	Actuation inhalation (120 doses)	45.5400 75.2800	0.3795 0.6273	100/200 mcg twice daily	0.76 to 1.25	277 to 458
Mometasone furoate (Asmanex Twisthaler)	200 mcg 400 mcg	Inhalant powder (60 doses)	36.1860 72.3840	0.6031 1.2064	200/400 mcg once daily	0.60 to 1.21	220 to 441
	400 mcg	Inhalant powder (30 doses)	36.1920	1.2064	400 mcg once daily	1.21	441
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	Inhalant powder (200 doses)	31.2700 63.8600 93.0000	0.1564 0.3193 0.4650	100/200/400 mcg twice daily	0.31 to 0.93	114 to 340
Beclomethasone dipropionate (QVAR)	50 mcg 100 mcg	Metered-dose aero inhalation (200 doses)	31.8100 63.4400	0.1591 0.3172	100 to 800 mcg daily, in two doses	0.32 to 2.54	116 to 927
ICS/LABA Combinations							
Budesonide/ Formoterol (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	Inhalant powder (120 doses)	65.7000 85.3800	0.5475 0.6990	100/6 mcg or 200/6 mcg twice daily	1.10 to 1.42	400 to 520
Fluticasone propionate/ Salmeterol (Advair)	125/25 mcg 250/25 mcg	MDI (120 doses)	97.4299 138.3141	0.8119 1.1526	125/25 mcg or 250/25 mcg twice daily	1.62 to 2.31	593 to 842
Fluticasone propionate/ Salmeterol (Advair Diskus)	100/50 mcg 250/50 mcg 500/50 mcg	Inhalation powder (60 doses)	81.3929 97.4299 138.3141	1.3565 1.6238 2.3052	100/50 mcg or 250/50 mcg or 500/50 mcg twice daily	2.71 to 4.61	991 to 1,684
Fluticasone furoate/ vilanterol trifenatate (Breo Ellipta)	100/25 mcg 200/25 mcg	Inhalant powder (30 doses)	82.2000 128.7400	2.7400 4.2913	100/25 mcg or 200/25 mcg once daily	2.74 to 4.29	1,001 to 1,567

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Mometasone furoate/ Formoterol fumarate (Zenhale)	50/5 mcg 100/5 mcg 200/5 mcg	MDI (120 doses)	Per dose[b] 91.1640 110.4960	0.5531 0.7597 0.9208	100/10 mcg 200/10 mcg 400/10 mcg twice daily	2.21 to 3.68	808 to 1,345
LTRAs							
Montelukast (generics)	4 mg 5 mg 10 mg	Chewable tab Chewable tab Tablet	0.3646 0.4280[a] 0.8195[a]	0.3646 0.4280 0.8195	Age 6 to 14: 5 mg daily Age 15+: 10 mg daily	0.43 to 0.82	156 to 299
Zafirlukast (Accolate)	20 mg	Tablet	0.7920[a]	0.7920	20 mg twice daily	1.58	579
LAMAs							
Tiotropium (Spiriva Respimat)	2.5 mcg	Solution for inhalation (60 inhal)	51.9000	0.8650	2 inhalations (2.5 mcg) once daily	1.73	632
Oral corticosteroids							
Prednisone (generic)	1 mg 5 mg 50 mg	Tablet	0.1066 0.0220 0.1735	0.09 to 0.26	20 to 60 mg daily for 5 to 10 days	0.09 to 0.26	*Per course:* 0.45 to 2.64

ICS = inhaled corticosteroid; inhal = inhalations; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MDI = metered-dose inhaler.

[a] Saskatchewan Formulary (accessed October 18, 2016).[23]

[b] British Columbia Formulary (accessed October 18, 2016).[24]

Source: Ontario Drug Benefit Formulary (accessed October 18, 2016) unless otherwise indicated.[25]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RESLIZUMAB RELATIVE TO STANDARD OF CARE?

Reslizumab Vs. SOC	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	$888,657 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.
Note: Based on the CADTH Common Drug Review deterministic base case.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RESLIZUMAB RELATIVE TO MEPOLIZUMAB?

Reslizumab Vs. Mepolizumab	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	Uncertain
Costs (total)						X
Drug treatment costs alone						X
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	Reslizumab is cost-saving compared with mepolizumab, based on the wholesale price of mepolizumab. Mepolizumab was recommended by CDEC with a requirement for a substantial price reduction, which will affect the analysis of comparative costs.					

CDEC = CADTH Canadian Drug Expert Committee; CE = cost-effectiveness; vs. = versus.
Note: Based on the CADTH Common Drug Review's best estimate.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS RESLIZUMAB RELATIVE TO OMALIZUMAB?

Reslizumab Vs. Omalizumab	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	Uncertain
Costs (total)						X
Drug treatment costs alone						X
Clinical outcomes						X
Quality of life						X
Incremental CE ratio or net benefit calculation	Reslizumab is more costly than omalizumab if the mean number of vials per patient for omalizumab is less than 2.83. A previous CDR report indicated an average of approximately 2.35 vials per patient, although there is some uncertainty regarding the calculation of vial usage.					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; vs. = versus.
Note: Based on CDR's best estimate.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 10: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The model lacked transparency and flexibility, which required some recoding to allow certain reanalyses to be undertaken.		
Was the material included (content) sufficient?		X	
Comments	Additional information was requested from the manufacturer, which did not entirely address some uncertainty regarding the clinical data used to inform the model.		
Was the submission well organized and was information easy to locate?		X	
Comments	See comments above.		

TABLE 11: AUTHORS' INFORMATION

Authors of the pharmacoeconomic evaluation submitted to the CADTH Common Drug Review			
☐ 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	

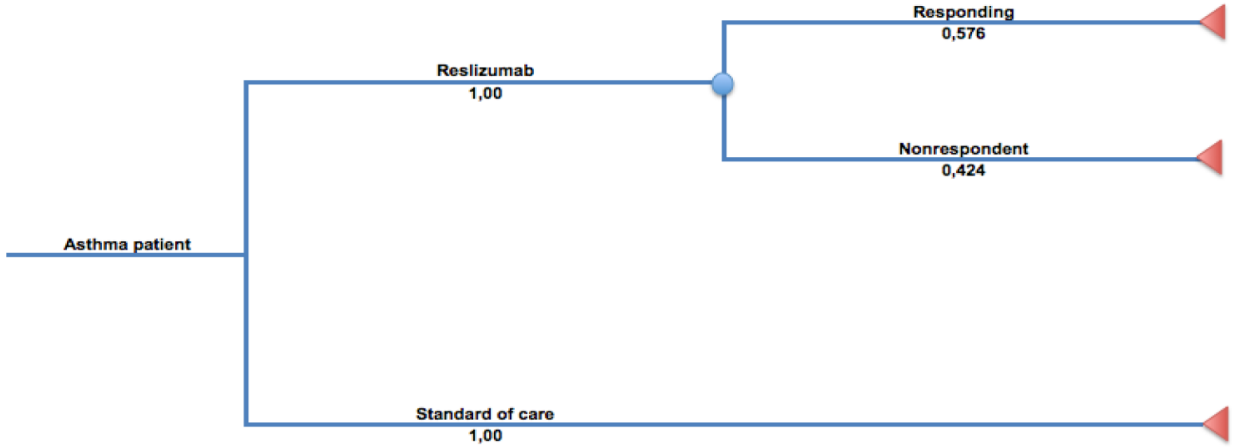
APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

No published health technology assessment reviews of reslizumab were identified. The National Institute for Health and Care Excellence (NICE) in the UK is currently reviewing reslizumab for the treatment of asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids, and NICE is scheduled to publish its findings in April 2017.[26]

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: MODEL STRUCTURE — DECISION TREE



Source: Manufacturer's pharmacoeconomic report.[2]

The Markov model comprises seven health states (Table 12). The interrelationships between health states can be seen in Figure 2. The manufacturer determined that a cycle length of two weeks was appropriate and consistent with previously published economic evaluations in asthma.[2]

TABLE 12: MARKOV MODEL HEALTH STATES

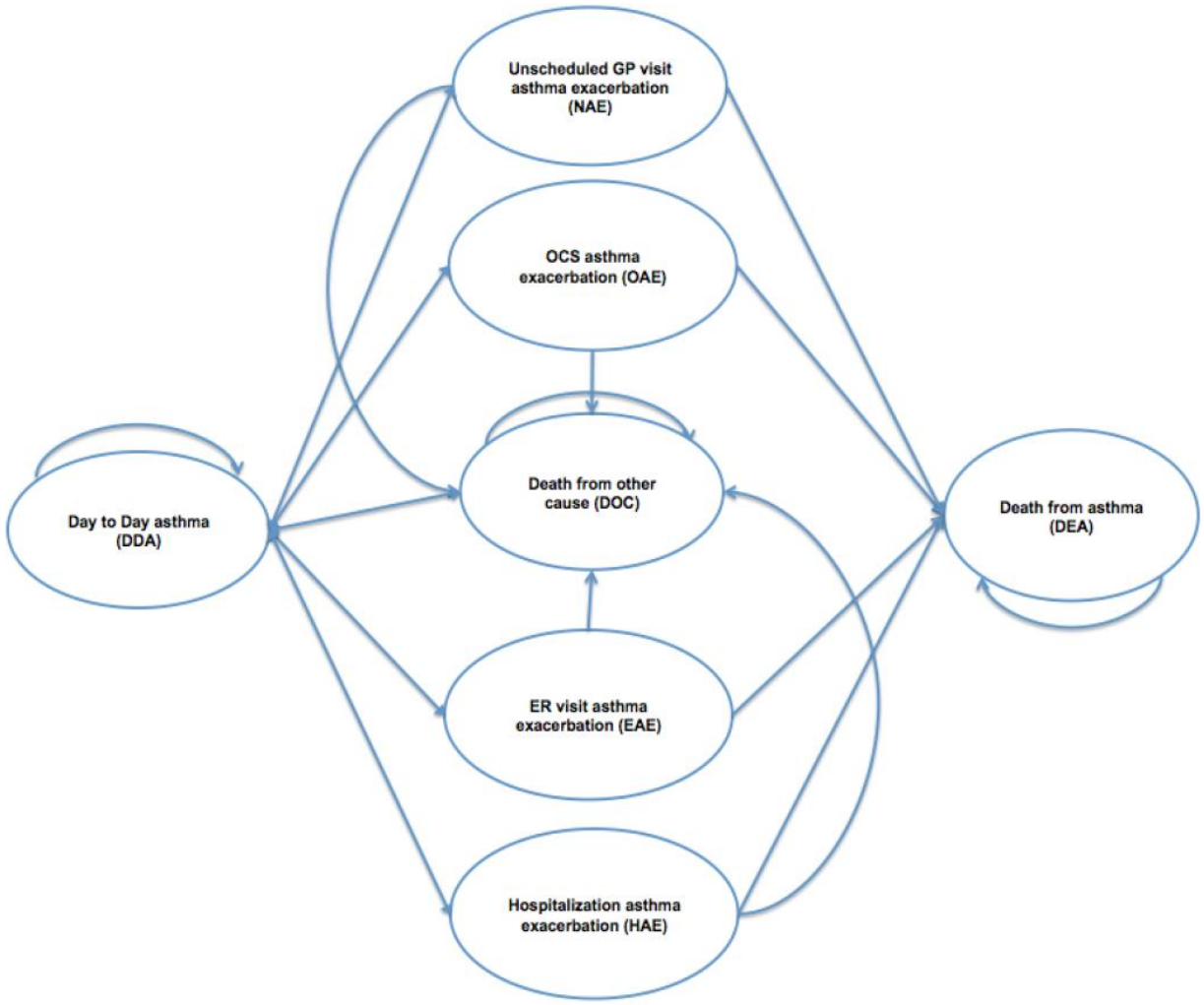
Health State	Description
Day-to-day asthma (DDA)	Asthma without exacerbation
Hospitalization for asthma exacerbation (HAE)	Asthma with exacerbation managed by hospitalization
ER for asthma exacerbation (EAE)	Asthma with exacerbation managed by a visit to the emergency department
OCS for asthma exacerbation (OAE)	Asthma with exacerbation managed by the use of OCS
Unscheduled GP visit for asthma exacerbation (NAE)	Asthma with exacerbation managed by an unscheduled visit to GP
Death from asthma (DEA)	Asthma-related death due to an exacerbation requiring an ER visit, hospitalization, unscheduled GP visit, or the use of OCS
Death from other causes (DOC)	Death unrelated to asthma

ER = emergency room; GP = general physician; OCS = oral corticosteroid.
Source: Reproduced from the manufacturer's pharmacoeconomic report.[2]

Patients enter the model in the day-to-day asthma (DDA) health state and remain there until they have an exacerbation event or die. Upon experiencing a moderate or severe exacerbation event, patients move into either the hospitalization for asthma exacerbation (HAE), emergency room visit for asthma exacerbation (EAE), unscheduled general physician visit for asthma exacerbation (NAE), or oral corticosteroids (OCSs) for asthma exacerbation (OAE) health state, depending on the event. A patient who dies without experiencing an exacerbation event will move into the death from other causes (DOC) health state. Patients remain in the exacerbation health state for one treatment cycle. Patients can transition back to the DDA health state from their exacerbation health state, or move to the death from

asthma (DEA) or DOC health states upon death. The manufacturer reported that the model structure is similar to other published models.[9,27]

FIGURE 2: MODEL STRUCTURE — MARKOV MODEL



ER = emergency room; GP = general physician; OCS = oral corticosteroid.
Source: Manufacturer's pharmacoeconomic report.[2]

TABLE 13: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy (response, exacerbations, etc.)	Clinical outcomes data were informed by 52-week trials of reslizumab (post hoc pooled analysis of Study 3082 and Study 3083).[2] Transition probabilities were derived from a post hoc analysis (unpublished) of the data for the subpopulation of interest for most parameters, and from the published study (full population) when subgroup information was not available. Data inputs from pooled analyses were based on populations of	CDR was unable to validate several of the manufacturer's inputs, as the methodology used to generate these data have not been published and were not adequately reported in materials submitted to CDR (clarified in the manufacturer's comments[18]). There were also differences in the data between Studies 3082 and

Data Input	Description of Data Source	Comment
	different sizes, but it was not always clear why population sizes differed across analyses. In Study 3082 and 3083, patients were treated for 52 weeks regardless of response at 16 weeks, and the resulting efficacy data were assumed to apply to responders as defined in the model.	3083 that were not well explained (e.g., exacerbation rates, different population sizes for included outcomes). There is uncertainty regarding appropriateness of the modelled response rate, due to the uncertain generalizability of the definition of "response" used in the model. Additional information was provided by the manufacturer, which clarified that response was based solely on a change in FEV_1 of 0.1 L.[18] Although changes to the response rate did not have a large effect on the cost-effectiveness results, the definition of response is likely to differ in clinical practice and may take into consideration other components (e.g., exacerbations, symptoms). The use of a change in FEV_1 that is lower than the MCID is unlikely to be appropriate, which results in uncertainty regarding the proportion of patients who would be considered responders in clinical practice.
Natural history — patient characteristics	Patient age, sex, and disease severity were based on the 2 phase III trials included in Castro et al.[6] Different patient characteristics for the 2 treatment cohorts were tested in sensitivity analyses.	Feedback from the CDR clinical expert indicated that patient characteristics in Studies 3082 and 3083 are largely applicable to the Canadian setting.
Utilities — DDA	Utility values for the DDA health state were based on ASUI questionnaire scores. The manufacturer noted the ASUI was used, as no EQ-5D values were available, and no mapping algorithm exists to transform the ASUI values to EQ-5D.	The ASUI has not been appropriately validated as a source of utility values. No justification for using different utility values for the DDA state based on treatment was provided.
Utilities — exacerbation states	Values for OAE, EAE, and HAE were based on published literature from Lloyd et al.[10] and Campbell et al.;[9] value for NAE was based on assumption.	The study by Lloyd et al.[10] included 112 patients, of whom only 27 had exacerbations (22 with no hospitalization, 5 with hospitalization). Thus, the small sample size may affect the generalizability of the results, especially given the substantial variance in the responses.
Adverse events	Incidence of AEs was not considered.	Feedback from CDR clinical expert suggested anaphylaxis should have

Data Input	Description of Data Source	Comment
		been considered in the economic model. It was likely appropriate that other AEs were not included in the model, based on the clinical data.
Asthma mortality	Rate of death due to asthma was derived from Watson et al.[28] and de Vries et al.[29]	Asthma mortality rate appears to have been overestimated by the manufacturer. An informal search did not locate any Canadian figures. CDR tested revised values in reanalyses.
All-cause mortality	Death from other causes was sourced from Statistics Canada's Canadian life tables.	Appropriate
Resource use		
Reslizumab	Reslizumab requires weight-based dose administration; the manufacturer used patient weight groups (per dose criteria) to determine resource use, although the source of this information was not stated.	The number of vials required differs based on patient weight, and the literature to verify the proportion of patients requiring different numbers of vials is limited; thus, there is uncertainty regarding the proportions used. The CDR clinical expert indicated that the real-world distribution of weights would likely be higher than that presented by the manufacturer; thus, CDR tested the impact of small incremental differences in patient weight distribution.
SOC	Proportion of patients receiving ICS + LABA, SABA, and OCS were based on Castro et al.[6]	Does not consider other potentially relevant treatments such as LAMAs and LTRAs; appropriate that use was the same between treatment groups
Costs		
Reslizumab	Provided by the manufacturer	
SOC	Ontario Drug Benefit Formulary[11] Costs for generics were used where available.	As noted above, the manufacturer did not consider other relevant treatments such as LAMAs and LTRAs. These could be potential comparators with reslizumab; however, there are no comparative data. Both treatments are indicated for use after treatment with an ICS + LABA, and clinical guidelines note that LAMAs can be used as Step 5 treatment, the same level at which biologics can be used.[5]

Data Input	Description of Data Source	Comment
		Additionally, although 65% of placebo patients in Studies 3082 and 3083 used LTRAs at baseline in the study, these were not considered in the cost of SOC.[30] There was uncertainty regarding lower SOC costs for the SOC arm compared with the reslizumab arm.
Administration	The manufacturer stated that it would cover all costs associated with administration of reslizumab, including a specialist nurse. SOC has no administration costs.	
Determination of response	Ontario Schedule of Benefits (A475 – specialist visit)[12]	Cost used is acceptable.
Exacerbation requiring hospitalization	CIHI PCE for asthma patients aged 19 to 58[13]	Cost used is accepted based on actual source (CMG 147).
Exacerbation requiring ER visit	OCCI for ambulatory care (J4501, J4581, J4591)[a]	
Exacerbation requiring OCS	Ontario Schedule of Benefits (C005), Ontario Drug Benefit Formulary/RAMQ Formulary[11,12,31]	There is some uncertainty regarding drug cost source, but in general, costs used are acceptable.
Exacerbation requiring GP visit	Ontario Schedule of Benefits (C005)[12]	Cost used is acceptable.

AE = adverse event; ASUI = Asthma Symptom Utility Index; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; DDA = day-to-day asthma; EAE = emergency room visit for asthma exacerbation; EQ-5D = EuroQol 5-Dimensions questionnaire; ER = emergency room; FEV_1 = forced expiratory volume in 1 second; GP = general physician; HAE = hospitalization for asthma exacerbation; ICS = inhaled corticosteroids; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MCID = minimal clinically important difference; NAE = unscheduled general physician visit for asthma exacerbation; OAE = oral corticosteroids for asthma exacerbation; OCCI = Ontario Case Costing Initiative; OCS = oral corticosteroid; PCE = patient cost estimator; RAMQ = Régie de l'assurance maladie du Québec; SABA = short-acting beta-agonist; SOC = standard of care.

[a] Previously accessible at http://www.occp.com/. Now accessible through the Ontario Health Data Branch (registration required).

TABLE 14: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
A 16-week period is appropriate to determine response.	Feedback from the CDR clinical expert noted that, in practice, current biologic therapies are more likely to be assessed at 6 months before a decision about maintaining or stopping treatment. If reslizumab were assessed at 6 months rather than 16 weeks, the cost-effectiveness analysis would underestimate the costs associated with reslizumab treatment, while the associated benefits would be uncertain. CDR was unable to revise the model to adjust for this scenario, given the model structure and lack of response data at week 26.
Treatment response was based on improvement from baseline in $FEV_1 \geq 0.1$ L.	Feedback from the CDR clinical expert suggested that the threshold for change in FEV_1 was lower than is generally used in clinical practice (> 0.2 L). The expert also noted that, in clinical practice, the definition of response may differ based on the speciality of the treating physician and on the presence/rate of exacerbations. Additionally, the CDR clinical reviewers identified sources that indicated a minimum patient perceivable improvement was a change of 0.23 L from baseline.[15]
The duration of reslizumab treatment for responders before switching to SOC is 10 years, based on previous economic evaluations for omalizumab.	While this appears to be consistent with other published economic evaluations (e.g., Norman et al.,[32] Faria et al.[33]), there is little long-term experience with reslizumab. The CDR clinical expert indicated that, if the patient continues to respond and in the absence of important toxicities, it is reasonable to expect the patient to continue biologic treatment indefinitely. Because of uncertainty in the long-term duration of treatment and response to reslizumab, this parameter was tested by CDR.
No patients on reslizumab discontinue treatment during the 10-year post-response period.	If a stopping rule were created for non-responders at different time points, this may improve the cost-effectiveness of reslizumab compared with SOC. However, long-term data to inform the rate of non-response over time among initial responders are unavailable.
Lifetime time horizon	In general, a lifetime time horizon is appropriate. However, CDR notes that a large amount of the incremental benefit compared with SOC occurs in the post-reslizumab treatment period (Table 20) as a result of more patients starting the post-treatment phase in a better health state and the corresponding survival benefit associated with reslizumab; this becomes apparent when the model time horizon is shortened to match the duration of treatment. This property of the model is associated with considerable uncertainty, as it requires an assumption that the effect of reslizumab observed in the 52-week trials can be extrapolated over the treatment period (10 years in the manufacturer's base case), with the divergence between reslizumab and SOC continuing to increase over the entire treatment period. There are no data to support this assumption.
A 2-week cycle time is appropriate.	Feedback from the CDR clinical expert suggested that 2 weeks was a clinically meaningful time interval to ensure that events are captured.

Assumption	Comment
Asthma exacerbations are the primary efficacy parameter of interest.	Appropriate based on feedback from the clinical expert consulted by CDR
Patients spend only 1 cycle in an exacerbation health state (OAE, EAE, HAE, or NAE) before moving back to the DDA state or to one of the death states (DEA, DOC).	Generally seen as appropriate based on feedback from clinical expert consulted by CDR, although it was unlikely that the total impact of a hospitalization (HAE) could be captured in only a 2-week period (4 weeks would have been more appropriate)
Transition probabilities for DDA to OAE, DDA to EAE, DDA to HAE, and DDA to NAE were derived from either post hoc data (unpublished) from the clinical trial for the adult subgroup (OAE, EAE, and NAE) or from the published study for the full population (HAE). A conversion rate for the 2-week cycle was applied based on a formula reported by Fleurence et al.[34]	CDR was unable to validate the transition probabilities based on the level of information presented by the manufacturer. CDR requested additional information from the manufacturer regarding the probability of transitioning to exacerbation health states. However, the response provided resulted in additional uncertainty as to whether the appropriate subgroups were analyzed, as the sample size provided did not match the subgroup sample size available to the CDR clinical team in its comparisons. CDR also noted that the subgroup analysis for exacerbations requiring hospitalization was from the full trial population rather than the subgroup representing the indicated population. Thus, there is some uncertainty in the generalizability of these results.
AEs were not considered in the analysis, as those reported in the clinical trial were generally not considered treatment-related.	The CDR clinical expert indicated that anaphylaxis may be an issue with reslizumab, based on its increased incidence in the clinical trials, and that the risk of this AE may be higher than with mepolizumab or omalizumab. The NMA results suggest that AEs occurred less frequently with reslizumab than omalizumab; however, CDR clinical reviewers noted limitations associated with the appraisal of safety data in short-term randomized controlled trials, which preclude any conclusions regarding comparative safety (see CDR Clinical Review Report, Appendix 7).
Patients can die from asthma.	Accepted
DOC was not adjusted for death from asthma.	Although asthma-related mortality represents a small fraction of overall mortality, given the lifetime time horizon, this may inappropriately reduce the number of patients toward the end of the model time horizon.
The manufacturer used different utility values for reslizumab and SOC for the DDA health state, based on a HRQoL questionnaire.	The ASUI questionnaire has not been appropriately validated as a primary source of utility values. It is not appropriate to assume a difference between treatments for the base health state (DDA).
The manufacturer's model did not consider that patients could have an exacerbation in the first 16 weeks.	This assumption is unlikely to be appropriate, as the trial indicated that approximately 15% to 35% of patients had an exacerbation in the first 16 weeks.[7,8]

AE = adverse event; ASUI = Asthma Symptom Utility Index; CDR = CADTH Common Drug Review; DDA = day-to-day asthma; DEA = death from asthma; DOC = death from other causes; EAE = emergency room visit for asthma exacerbation; FEV_1 = forced expiration volume in 1 second; HAE = hospitalization for asthma exacerbation; HRQoL = health-related quality of life; NAE = unscheduled physician visit for asthma exacerbation; OAE = oral corticosteroids for asthma exacerbation; SOC = standard of care.

The manufacturer undertook four additional scenario analyses for the reslizumab plus standard of care (SOC) versus SOC comparison: 1) a scenario analysis based on the full population from the Castro et al.[6] study; 2) a scenario analysis of patients with two exacerbations (i.e., more severe subset); 3) a scenario in which the utility value for DDA is the same for both treatment groups; and 4) a scenario with a different duration of reslizumab.

Additionally, the manufacturer undertook deterministic and probabilistic sensitivity analyses (PSAs) to test the robustness of the model results. The deterministic sensitivity analysis was undertaken on key clinical parameters, health-state utilities, exacerbation rates (using the lower and upper bounds of the 95% confidence interval), and cost inputs (varying the values by 25% in either direction). The PSA was undertaken using a Monte Carlo simulation of 1,000 patients using gamma distributions for the cost parameters and beta or symmetric triangular distribution for probabilities and utilities.

Manufacturer's Results

The manufacturer's analysis indicated that, over a lifetime time horizon (patients on reslizumab for 10 years), patients who received reslizumab plus SOC obtained more quality-adjusted life-years (QALYs) than with SOC alone, although at a substantially greater cost (Table 15).

TABLE 15: MANUFACTURER'S BASE-CASE RESULTS

	Total Costs	Incremental Cost of Reslizumab	Total QALYs	Incremental QALYs of Reslizumab	Incremental Cost per QALY
SOC	$32,650		4.01		
Reslizumab + SOC	$139,058	$106,407	4.42	0.42	$256,090

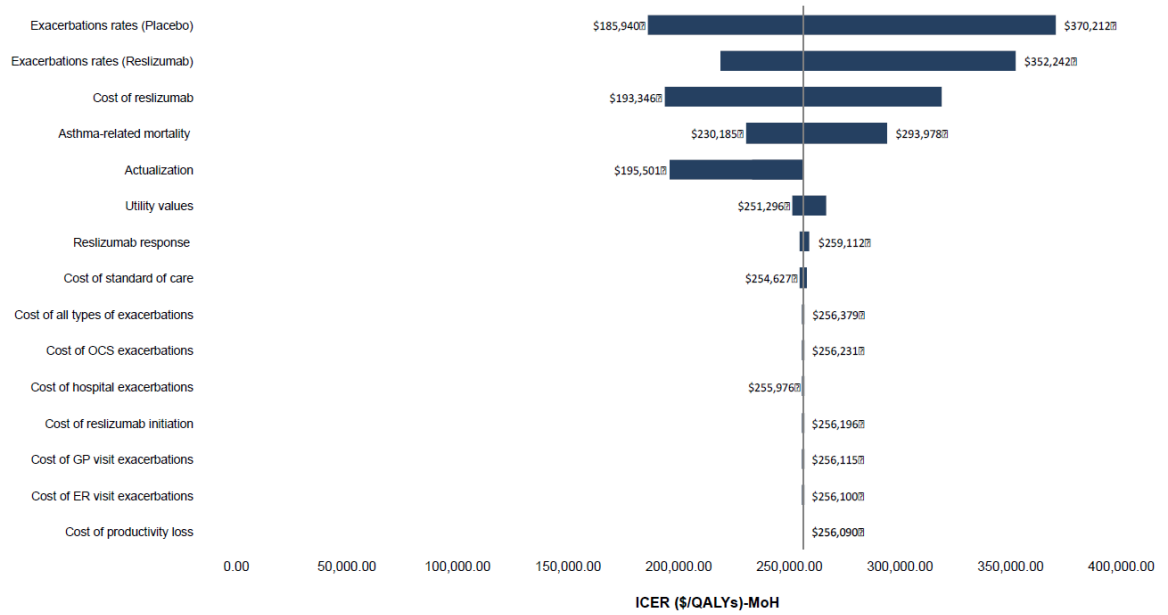
QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

The manufacturer's scenario analyses indicated that each of the following scenarios affects the incremental cost-utility ratio (ICUR):

- If the full trial population in Studies 3082 and 3083 is used (including patients younger than 18 years), the ICUR increases to $294,802 per QALY.
- If a population with more severe asthma (two or more exacerbations) is used, the ICUR is reduced to $203,441 per QALY.
- If the health-state utility for DDA is assumed to be the same for both treatments, the ICUR increases to $330,781 per QALY.
- If the treatment duration is shortened to five years, the ICUR is reduced to $189,081 per QALY.

The manufacturer's deterministic sensitivity analysis indicated that the ICUR ranged from $185,940 per QALY to $370,212 per QALY (Figure 3). The upper and lower bounds were based on the revised exacerbation rate for SOC. Other inputs that affected the results were the exacerbation rate for reslizumab, the cost of treatment with reslizumab, and the discount rate.

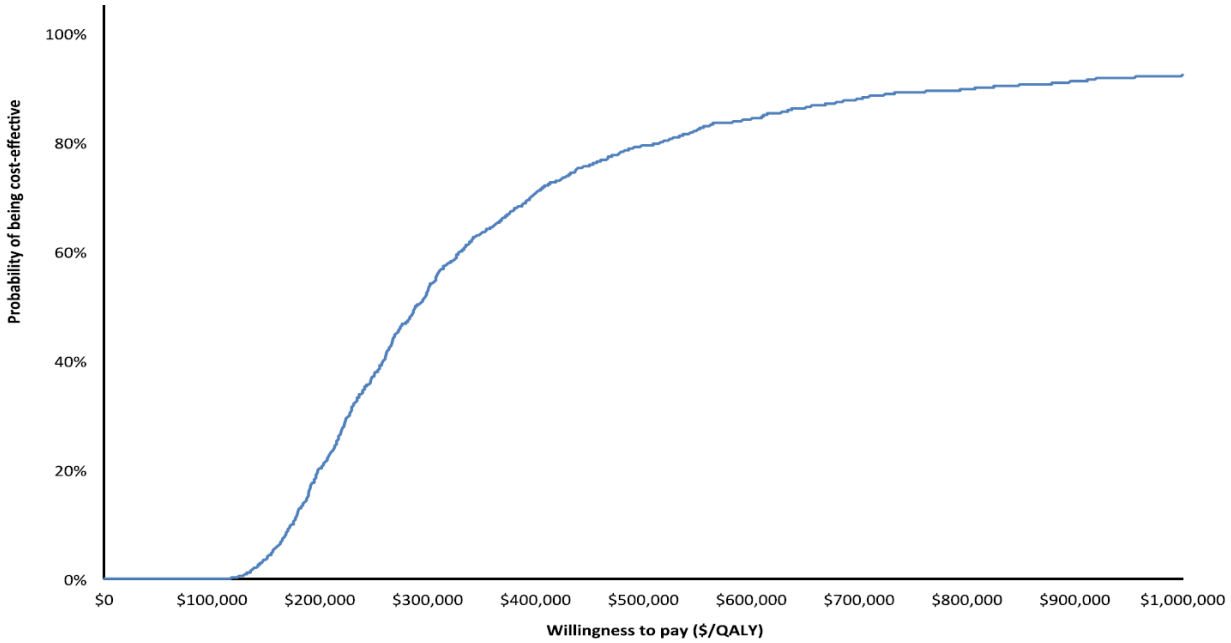
FIGURE 3: TORNADO DIAGRAM FOR DETERMINISTIC SENSITIVITY ANALYSIS



ER = emergency room; GP = general physician; ICER = incremental cost-effectiveness ratio; MoH = Ministry of Health perspective; OCS = oral corticosteroid; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic report.[2]

The manufacturer's PSA was primarily presented as a cost-effectiveness acceptability curve (CEAC) and scatter plot. The CEAC indicated that, at a threshold of $100,000 per QALY, there was a 0% probability that reslizumab plus SOC is cost-effective. At a threshold of $150,000 per QALY, there is a 2% probability that reslizumab is cost-effective, increasing to 50% at a threshold of $300,000 per QALY (Figure 4).

FIGURE 4: COST-EFFECTIVENESS ACCEPTABILITY CURVE



QALY = quality-adjusted life-year.
Source: manufacturer's pharmacoeconomic report.[2]

The manufacturer incorrectly calculated the mean probabilistic ICUR as $561,228 per QALY. However, when calculated appropriately based on the mean incremental costs and QALYs, the mean probabilistic ICUR was $304,167 per QALY (Table 16).

TABLE 16: RESULTS OF THE MANUFACTURER'S PROBABILISTIC ANALYSIS

	Total Costs	Incremental Cost of Reslizumab	Total QALYs	Incremental QALYs of Reslizumab	Incremental Cost per QALY
Probabilistic results (1,000 simulations)					
SOC	$31,699		4.243		
Reslizumab + SOC	$142,338	$110,639	4.606	0.3637	$304,167

QALY = quality-adjusted life-year; SOC = standard of care.
Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

The CADTH Common Drug Review (CDR) undertook reanalyses of the manufacturer's PSA using 5,000 simulations, which produced similar results (mean ICUR = $293,000 per QALY, 52% probability of being cost-effective when the threshold is $300,000 per QALY).

Manufacturer's Cost-Minimization Analysis

The manufacturer undertook additional analyses comparing the cost of reslizumab with that of mepolizumab and omalizumab. Omalizumab was included although the manufacturer noted that omalizumab is an anti-immunoglobulin E (IgE) indicated for moderate to severe allergic asthma, which targets a different phenotype compared with reslizumab, although there is some degree of overlap between the indicated populations, according to the clinical expert consulted by CDR.

The manufacturer undertook this form of analysis based on the results of a manufacturer-sponsored network meta-analysis,[4] which reported that reslizumab was comparable to mepolizumab and omalizumab in terms of efficacy and safety.

The manufacturer reported that the annual cost of reslizumab was calculated based on the weight distribution of patients in the target population, although the source of these data was not specified. Based on the numbers of patients cited, the distribution does not appear to be solely from the patients in Studies 3082 and 3083. The number of vials of reslizumab used was then based on the proportion of patients in each of the weight ranges (Table 17).

TABLE 17: DETERMINATION OF WEIGHT-BASED DOSE CALCULATIONS

Number of Patients	Patient Weight Ranges (kg)	Dose Distribution
[redacted]	< 34	[redacted]
[redacted]	34 to 66.9	[redacted]
[redacted]	67 to 99.9	[redacted]
[redacted]	100 to 133.9	[redacted]
[redacted]	> 134	[redacted]

Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

The manufacturer determined the cost of mepolizumab from McKesson and QuintilesIMS Delta PA (wholesale price: $1,938.46 per vial). Mepolizumab utilization was determined based on the product monograph dosage of 100 mg every four weeks. The cost of omalizumab was from the Ontario Drug

Benefit Exceptional Access Formulary ($624.24 per vial). Omalizumab utilization was based on information provided to the manufacturer by Telus Health (September 2015), which indicated an average of [redacted] vials per month.[2] The relative annual costs for each of the treatments are reported in Table 18.

TABLE 18: MANUFACTURER'S COST-MINIMIZATION ANALYSIS RESULTS

Treatment	Annual Cost	Incremental Cost (vs. reslizumab)
Reslizumab	$23,096	-
Mepolizumab	$25,269	+$2,174
Omalizumab	$26,202	+$3,107

Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

CADTH Common Drug Review Reanalyses

CDR identified several limitations and parameters that were associated with uncertainty in the manufacturer's cost-utility analysis. Accordingly, CDR undertook several one-way and multi-way reanalyses to test the robustness of the manufacturer's results.

Duration of reslizumab use and time horizon. CDR tested various durations of treatment, as there is uncertainty as to how long patients who initially respond to treatment with reslizumab will continue therapy. To address the observation that much of the QALY gains associated with reslizumab were accrued after treatment discontinuation, CDR tested various time horizons aligned with the duration of treatment.

Utility values for day-to-day asthma state. The manufacturer assumed that patients receiving treatment with reslizumab had a better quality of life in the DDA state than patients who were receiving placebo. This is not an appropriate assumption and is not representative of the data from the clinical trials, as in none of the three quality-of-life scales did reslizumab exceed the minimal clinically important difference (MCID; 0.5 points for the Asthma Control Questionnaire and Asthma Quality of Life Questionnaire, and 0.09 for the Asthma Symptoms Utility Index [ASUI]). CDR therefore undertook reanalyses using the same utility value for DDA for patients, regardless of treatment (using the reslizumab values). As well, the manufacturer's direct use of values derived from a disease-specific quality-of-life measure (ASUI) as utility values is not appropriate. Other published values could have been used for the day-to-day health state. Although these values were mapped to a utility instrument (EuroQol 5-Dimensions questionnaire [EQ-5D]) from disease-specific quality-of-life questionnaires (which is not ideal), this is still preferable to direct use of the ASUI values. CDR tested various published utility values for the DDA health state.[10,35]

Definition of response. Feedback from the CDR clinical expert suggested that the definition of response may not be appropriate, as a threshold of a 0.1 L improvement in forced expiratory volume in one second is considered lower than the MCID in clinical practice (0.23 L),[15] and that other criteria, such as exacerbations, may affect the determination of response. As well, the CDR clinical expert suggested that response may be not be assessed until six months, based on current practice for omalizumab. CDR tested various response rates at 16 weeks, and, while these did not have a large impact on the results, the impact of extending the trial period could not be tested without substantial revisions to the model structure and without efficacy data supporting response rates at 26 weeks.

Asthma mortality rate. CDR noted that the asthma mortality rate was derived from two studies in the UK that appeared to indicate that the asthma mortality rate was below 1%, yet the manufacturer's calculation resulted in a mortality rate of 1.44%, which is likely to be an overestimate. The clinical expert consulted by CDR agreed that this was likely an overestimate. CDR therefore tested an asthma mortality rate of 1% per year.

Cost calculation for SOC. The manufacturer underestimated the cost of SOC in the SOC arm compared with the reslizumab arm. CDR revised the SOC costs so that these were the same in both treatment arms.

Patient weight distribution. The manufacturer indicated that the patient weight distribution used for costing of reslizumab was based on the weight distribution of patients in the target population; however, given the limited data reported in the Clinical Study Report and publication, this could not be easily verified. Feedback from the CDR clinical expert indicated that there may be a slightly higher proportion of patients in practice in the higher weight ranges (especially given the indication for adult patients), which would increase total costs associated with reslizumab. CDR tested revised assumptions regarding patient weight based on feedback provided by the CDR clinical expert (Table 19). This affects the cost-minimization analysis as well.

TABLE 19: WEIGHT-BASED DOSE CALCULATIONS

Weight Group	Manufacturer Proportion[a]	CDR Revised Assumption
0 to 33.9 kg	[redacted]	0%
34 to 66.9 kg	[redacted]	28%
67 to 99.9 kg	[redacted]	60%
100 to 133.9 kg	[redacted]	11%
134 kg and above	[redacted]	1%
Total	100%	100%

CDR = CADTH Common Drug Review.
[a] Based on a distribution of 928 patients.
Source: Adapted from the manufacturer's pharmacoeconomic report.[2]

TABLE 20: CDR ONE-WAY AND MULTI-WAY DETERMINISTIC REANALYSIS RESULTS

Parameter (Results Reported as Reslizumab vs. SOC)	Incremental Cost	Incremental QALY	ICUR (per QALY)
Manufacturer's base case	**$106,407**	**0.42**	**$256,090**
Treatment duration and time horizon			
Duration of treatment = 5 years, time horizon per base case	$67,536	0.36	$189,081
Duration of treatment = 15 years, time horizon per base case	$131,104	0.45	$289,690
Duration of treatment and time horizon = 10 years	$103,235	0.27	$379,326
Duration of treatment and time horizon = 15 years	$129,069	0.38	$342,895
Duration of treatment and time horizon = 5 years	$61,727	0.13	$461,976
Utility values:			
DA for reslizumab and SOC based on Ismaila et al.[35](0.827)	$106,407	0.30	$359,430

Parameter (Results Reported as Reslizumab vs. SOC)	Incremental Cost	Incremental QALY	ICUR (per QALY)
DDA for reslizumab and SOC based on Lloyd et al.[10] (0.890)	$106,407	0.32	$330,781
Asthma mortality rate:			
Revised asthma mortality rate = 1%	$107,743	0.35	$304,884
Revised asthma mortality rate = 2%	$104,637	0.48	$219,075
Response rate in first 16 weeks:			
Revised response rate for reslizumab = 30%	$59,350	0.22	$264,239
Revised response rate for reslizumab = 40%	$76,400	0.29	$260,063
Revised response rate for reslizumab = 50%	$93,449	0.36	$257,478
Revised response rate for reslizumab = 65%	$119,024	0.47	$255,038
SOC cost calculation:			
SOC cost revised (same for reslizumab and SOC)	$105,895	0.42	$254,856
Reslizumab cost:			
Revised proportion of patient weights	$109,487	0.42	$263,501

CDR = CADTH Common Drug Review; DDA = day-to-day asthma; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

The CDR base case was based on the manufacturer's base-case model with the following revisions:

- Treatment duration and time horizon were 10 years.
- DDA utility values were the same for reslizumab and SOC, and based on the values reported in Lloyd et al.[10]
- Asthma mortality rate was revised to 1%.
- Cost of SOC was assumed to be the same in both the reslizumab + SOC and SOC treatment groups.
- The distribution of patient weights was revised per Table 19.
- The PSA was undertaken using 5,000 simulations.

TABLE 21: CADTH COMMON DRUG REVIEW DETERMINISTIC AND PROBABILISTIC BASE-CASE RESULTS

Parameter (Results Reported as Reslizumab vs. SOC)	Incremental Cost	Incremental QALY	ICUR (per QALY)
Manufacturer's base case	**$106,407**	**0.42**	**$256,090**
Multi-way (CDR deterministic base case)			
Duration of treatment and time horizon = 10 years, DDA utility values for reslizumab and SOC based on Lloyd et al.,[10] asthma mortality rate = 1%, revised SOC cost, revised patient weight	$107,603	0.12	$888,657
Multi-way (CDR probabilistic base case: 5,000 simulations)			
Duration of treatment and time horizon = 10 years, DDA utility values for reslizumab and SOC based on Lloyd et al.,[10] asthma mortality rate = 1%, revised SOC cost, revised patient weight	$111,423	0.0949	$1,174,109

CDR = CADTH Common Drug Review; DDA = day-to-day asthma; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Additionally, CDR undertook an exploratory analysis of the CDR deterministic reanalysis base case. This analysis compared reslizumab with a long-acting muscarinic antagonist (LAMA; in this example, tiotropium was used) under the most optimistic scenario for reslizumab, in which it was assumed that all SOC-alone patients received a LAMA in addition to their current treatment (thereby incurring the cost of the LAMA), but accrued no additional benefit compared with SOC alone. The results are presented in Table 22.

TABLE 22: CADTH COMMON DRUG REVIEW EXPLORATORY ANALYSIS RESULTS

Parameter (Results Reported as Reslizumab vs. SOC)	Incremental Cost	Incremental QALY	ICUR (per QALY)
Exploratory analysis of reslizumab vs. LAMA (tiotropium)			
Based on the CDR deterministic base case, with additional acquisition costs for tiotropium (based on the Ontario Drug Benefit Formulary[25]) in the SOC-alone arm.	$104,560	0.12	$866,260

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LAMA = long-acting muscarinic antagonist; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

CDR also conducted reanalyses of the submitted cost analysis for reslizumab versus omalizumab and mepolizumab, based on the following limitations identified:

- Per the above reanalysis of the cost-utility analysis, CDR revised the patient weight distribution for the cost analysis.
- The assumed dose of omalizumab in the model may have been overestimated, which impacts the comparative costs of mepolizumab and omalizumab. The manufacturer's assumption of [redacted] vials per 28-day cycle may be an overestimate, based on a CDR review of QuintilesIMS data, which indicates 2.32 to 2.35 vials per claim.[17] However, CDR notes that the there is some uncertainty regarding the calculation of vial usage due to the lack of information on the number of days' supply, and that there appear to be differences in usage between jurisdictions. Based on the manufacturer's assumed weight-based stratification of annual costs for reslizumab, the average number of vials per dose of omalizumab would be 2.83 vials or fewer per 28-day cycle, rendering it less costly than reslizumab.
- CDR previously reviewed mepolizumab and indicated that a reduction of 80% to 89% in the confidential price was required for mepolizumab to be cost-effective at a threshold of $50,000 per QALY.[19] CDR considered three price-reduction scenarios for mepolizumab based on its wholesale list price. However, these are for informational purposes only and were not considered in the CDR base-case reanalysis, as they do not reflect actual prices.

TABLE 23: CADTH COMMON DRUG REVIEW REANALYSES OF MANUFACTURER'S COST-MINIMIZATION ANALYSIS RESULTS

Scenario	Reslizumab	Mepolizumab	Omalizumab
Manufacturer's base case	$23,096	$25,269	$26,202
Incremental difference (comparator vs. reslizumab)		+$2,174	+$3,107
Revised patient weight (Table 19)	$23,778	$25,269	$26,202
Incremental difference (comparator vs. reslizumab)		+$1,491	+$2,424
Revised omalizumab use (2.35 vials)	$23,096	$25,269	$19,123
Incremental difference (comparator vs. reslizumab)		+$2,174	–$3,973
Combined analysis	**$23,778**	**$25,269**	**$19,123**
Incremental difference (comparator vs. reslizumab)		**$1,491**	**–$4,655**
Additional reanalyses			
Price reduction for mepolizumab (80%)	$23,096	$5,054	Per the manufacturer's base case
Incremental difference (comparator vs. reslizumab)		–$18,042	
Price reduction for mepolizumab (50%)	$23,096	$12,635	
Incremental difference (comparator vs. reslizumab)		–$10,461	
Price reduction for mepolizumab (30%)	$23,096	$17,688	
Incremental difference (comparator vs. reslizumab)		–$5,408	

vs. = versus.

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