

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Benralizumab (Fasenra)

(AstraZeneca Canada Inc.)

Indication: An add-on maintenance treatment of adult patients with severe eosinophilic asthma.

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Abbreviations

AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
CDR	CADTH Common Drug Review
EQ-5D	EuroQoL 5-Dimensions questionnaire
ER	emergency room
ICS	inhaled corticosteroid
ICUR	incremental cost-utility ratio
LABA	long-acting beta2 agonist
OCS	oral corticosteroid
QALY	quality-adjusted life-year
SOC	standard of care

Table 1: Summary of the Manufacturer’s Economic Submission

Drug Product	Benralizumab (Fasenra)
Study Question	To determine the cost-effectiveness of benralizumab as add-on therapy to standard of care (SOC) compared with SOC alone, or with SOC plus biologics approved for use in severe asthma (mepolizumab, omalizumab) for the treatment of a Canadian population of adults with severe uncontrolled eosinophilic asthma
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with severe uncontrolled eosinophilic asthma
Treatment	Benralizumab, 30 mg administered via subcutaneous injection once every 4 weeks for the first 3 doses and once every 8 weeks thereafter, in addition to SOC (high-dose ICS + LABA ± OCS)
Outcome	Quality-adjusted life-years (QALY)
Comparators	<ul style="list-style-type: none"> • SOC alone (high-dose ICS + LABA ± OCS, without add-on biologic therapy) • Mepolizumab + SOC • Omalizumab + SOC
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (approximately 50 years)
Results for Base Case	<p>Benralizumab + SOC vs. SOC (population with 21% chronic OCS): \$201,172 per QALY</p> <p>Benralizumab + SOC vs. SOC (population with 100% chronic OCS use): \$42,223 per QALY</p> <p>Benralizumab + SOC vs. Mepolizumab + SOC: \$19,865 per QALY</p> <p>Benralizumab + SOC vs. Omalizumab + SOC: \$40,241 per QALY</p>
Key Limitations	<ul style="list-style-type: none"> • Modelled population had a different profile than would be expected in Canadian patients with severe eosinophilic asthma. Specifically, the proportion of patients with chronic OCS use was assumed to be higher in the model (21%) than expected in Canadian practice. • Manufacturer assumed a reduction in exacerbations necessitating an ER visit or hospital admission led to a survival benefit with benralizumab that has not been demonstrated in trials (based on reduced exacerbations). This modelling approach may overestimate the benefit of benralizumab. • Definition of response used in the economic model may not be aligned with the definition in CDR-participating drug plans. Further, it is not clear that all patients that do not achieve response (i.e., “non-response”) would stop treatment with benralizumab. • Utility values for the day-to-day asthma health states in the model were assumed to differ between biologic treatment and SOC at baseline. Additionally, increased utility for responders to biologic treatment may overestimate treatment benefit. • The relative safety and efficacy of benralizumab compared with other biologics is unknown; the population eligible for treatment may not be identical among biologics.
CDR Estimates	<ul style="list-style-type: none"> • The CDR base case assumed: 5% of patients with chronic OCS use, the same day-to-day utility values for biologic and SOC, no difference in asthma-related mortality between comparators, and equal efficacy for benralizumab compared with the other biologic treatments. The incremental cost-utility ratio (ICUR) for benralizumab + SOC was \$1,534,803 per QALY vs. SOC alone. A price reduction of > 95% is required for the ICUR to fall below \$50,000 per QALY. • The ICUR for the 100% chronic OCS population was \$62,209 per QALY. A price reduction of approximately 15% is required for the ICUR to fall below \$50,000 per QALY. • Benralizumab + SOC is more costly and as effective as mepolizumab + SOC (\$5,720), and omalizumab + SOC (\$9,439). A sequential analysis could not be undertaken given the manufacturer’s model structure. A price reduction of 4% to 7% (or 1% to 3% with administration costs) is required for benralizumab to be no more costly than mepolizumab and omalizumab respectively.

CDR = CADTH Common Drug Review; ER = emergency room; ICS = inhaled corticosteroid; ICUR = incremental cost-utility ratio; LABA = long-acting beta2 agonist; OCS = oral corticosteroid; QALY = quality-adjusted life-year; SOC = standard of care.

Drug	Benralizumab (Fasenra)
Indication	An add-on maintenance treatment of adult patients with severe eosinophilic asthma
Reimbursement Request	For add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose ICS and one or more additional asthma controller(s) (e.g., LABA), if one of the following clinical criteria are met: <ol style="list-style-type: none"> 1. Blood eosinophil count of ≥ 300 cells/μL and have experienced two or more clinically significant asthma exacerbations in the past 12 months, or 2. Blood eosinophil count of ≥ 150 cells/μL and are treated chronically with OCS.
Dosage Form(s)	30 mg subcutaneous injection
NOC Date	February 22, 2018
Manufacturer	AstraZeneca Canada Inc.

Executive Summary

Background

Benralizumab (Fasenra) is a targeted, humanized monoclonal antibody indicated as an add-on maintenance treatment of adult patients with severe eosinophilic asthma.¹ The recommended dose is 30 mg administered via subcutaneous injection once every four weeks for the first three doses, and then once every eight weeks thereafter.¹ It is supplied as a solution for injection in a 30 mg/mL syringe. The submitted price of benralizumab is \$3,876.92 per syringe injection,² resulting in an annual cost of \$31,015 in year 1 and \$25,200 in subsequent years.

The requested reimbursement criteria are: for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with a high-dose inhaled corticosteroid (ICS) and one or more additional asthma controller(s) (e.g., long-acting beta2 agonist [LABA]), if: blood eosinophil count of ≥ 300 cells/ μ L AND have experienced two or more clinically significant asthma exacerbations in the past 12 months; or blood eosinophil count of ≥ 150 cells/ μ L AND are treated chronically with oral corticosteroids (OCS).²

The manufacturer submitted cost-utility analyses that assessed benralizumab + standard of care (SOC: high-dose ICS + LABA \pm OCS) in adult patients with severe uncontrolled eosinophilic asthma over a lifetime (approximately 50-year) time horizon from the perspective of the Canadian health care payer.³ The manufacturer presented four base cases, based on two distinct patient populations: one representing a combination of the two populations based on the reimbursement request (considering a proportion of patients with chronic OCS use), and the other focusing on the second component of the request (all patients with chronic OCS use). For the combined population, the manufacturer presented three separate analyses that compared benralizumab + SOC individually with SOC alone, mepolizumab + SOC, and omalizumab + SOC. For the population considering chronic OCS patients only, benralizumab + SOC was compared with SOC alone. These analyses were

undertaken separately based on an assumption of different baseline characteristics and efficacy inputs (treatment response and exacerbation rate) for each individual comparison. Data from the clinical trials of benralizumab were used to inform the model. Specifically, the ZONDA trial was used to inform the chronic OCS use population, while data from a pooled analysis of the CALIMA and SIROCCO studies were used to inform the non-chronic OCS use population for the analyses comparing benralizumab + SOC with SOC alone. Data from two separate matched-adjusted indirect comparisons were used to inform the comparison of benralizumab + SOC with two currently available biologic treatments (mepolizumab and omalizumab). Different baseline characteristics, including the proportion of patients on chronic OCS, were assumed based on the analyses. The manufacturer developed a Markov model that included four health states: day-to-day asthma receiving a biologic + SOC, day-to-day asthma receiving SOC alone, a general exacerbation health state (with tunnel states based on type of exacerbation: requiring OCS burst treatment, emergency room [ER] visit or hospital admission), and mortality (which included increased mortality for exacerbations requiring ER or hospital visit). Pooled EuroQoL 5-Dimensions questionnaire (EQ-5D) scores from SIROCCO and CALIMA (patients not on chronic OCS) or ZONDA (patients on chronic OCS, EQ-5D mapped from the Asthma Quality of Life Questionnaire) were used to inform the day-to-day health state utility values. The same utilities from benralizumab were applied to mepolizumab and omalizumab. Other inputs such as costs, utility decrements for exacerbation and chronic OCS use, and mortality were obtained from published literature.³

The manufacturer reported that for the combined chronic/non-chronic OCS use population, the incremental cost-utility ratios (ICURs) for benralizumab + SOC were:

- \$201,172 per quality-adjusted life year (QALY) when compared with SOC alone
- \$19,865 per QALY when compared with mepolizumab + SOC
- \$40,241 per QALY when compared with omalizumab + SOC.

When assuming 100% chronic OCS use, the ICUR for benralizumab + SOC compared with SOC alone was \$42,223 per QALY.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several key limitations with the submitted analysis. The lack of comparative clinical information to allow a sequential analysis that compared benralizumab, SOC, mepolizumab, and omalizumab, and the limitations of the submitted model structure, were identified as large limitations with the submitted economic evaluation, which limited the reanalyses that CDR was able to undertake.

Based on what could be assessed, CDR identified several limitations with the submitted model. First, the manufacturer assumed that patients requiring acute OCS therapy had the same response to therapy as patients on chronic daily OCS treatment, and a higher proportion of patients were on chronic OCS therapy than is likely to occur in Canadian clinical practice. This assumption is not appropriate given the difference in treatment effect for chronic OCS users (based on the ZONDA trial) and the treatment effect observed in the CALIMA and SIROCCO trials, in which 20% of patients were on acute OCS treatment. Second, the application of different utility values for a day-to-day health state based on treatment is not appropriate, nor is the assumption of an increment for responders to biologic therapy and not SOC. Third, the manufacturer assumed that increased mortality would be observed when patients had an exacerbation (ER visit or hospital admission) and that reduction in exacerbations would lead to a survival benefit. A survival benefit has not

been demonstrated in the benralizumab trials, and the CDR clinical expert noted that asthma-related mortality is very uncommon in treatment-adherent patients. Fourth, it is not clear that the “non-response” criterion would be operationalized in the same way in real-world use; it is likely that many patients may remain on benralizumab even if they met the trial definition of “non-response.”

The limitations with the largest impact on the results were the utility value assumptions, the proportion of patients at baseline on chronic OCS use, and the assumed mortality benefit associated with reduced exacerbations. CDR attempted to address these issues in reanalyses that assume 5% chronic OCS use (based on feedback from a clinical expert consulted by CDR), the same baseline utility values between treatment groups in the day-to-day asthma health states, and no difference in mortality between comparators.

In the CDR base case, the ICUR for benralizumab + SOC was \$1,534,803 per QALY when compared with SOC alone. A price reduction of more than 95% for benralizumab would be required to reduce the ICUR to \$50,000 per QALY. When considering the population on chronic OCS use, CDR reanalysis indicated an ICUR of \$62,209 per QALY; a 15% price reduction is required to achieve an ICUR of \$50,000 per QALY.

The comparison of benralizumab with other biologics used in asthma was hindered by differences in indication (particularly versus omalizumab) and by the lack of head-to-head trials. While an indirect comparison was conducted, CDR clinical reviewers identified several limitations with the submitted indirect comparison. As such, under the assumption of similar safety and efficacy, benralizumab was more costly than mepolizumab and omalizumab, as the drug acquisition cost of benralizumab is higher than the other two biologics. The price of benralizumab would need to be reduced by 4% to be less costly than mepolizumab and 7% to be less costly than omalizumab (or 1% to 3% with administration costs).

Conclusions

The primary limitations identified in the review were the lack of comparative clinical information for the population of interest that would allow a sequential analysis and whether the model presented adequately covers the full Health Canada–indicated population.

CDR reanalyses indicated the ICUR for benralizumab + SOC versus SOC alone is likely to be approximately \$1.5 million per QALY. Results were highly sensitive to utility value assumptions, continued usage of biologics for nonresponders, and the proportion of chronic OCS users. When considering only patients with chronic OCS use (at least six months), the ICUR for benralizumab + SOC compared with SOC alone is approximately \$62,000 per QALY. A price reduction of more than 95% is required to achieve an ICUR below \$50,000 per QALY for the reimbursement request population; while a price reduction of 15% is required to achieve an ICUR below \$50,000 per QALY for the population that is on chronic OCS use.

Benralizumab was more costly and as effective as mepolizumab and omalizumab. A price reduction of 4% to 7% (or 1% to 3% with administration costs) is required for benralizumab to be no more costly than other biologics when considering the combined population.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted cost-utility analyses assessing benralizumab + standard of care (SOC: high-dose inhaled corticosteroid [ICS] + long-acting beta2 agonist [LABA] ± oral corticosteroid [OCS]) in patients with severe uncontrolled eosinophilic asthma.³ The time horizon was a patient lifetime (approximately 50 years) with a 28-day cycle length, and the Canadian public payer perspective was used.

The manufacturer presented four base cases, based on two distinct patient populations: one representing a combination of the two populations based on the reimbursement request (considering a proportion of patients with chronic OCS use, the remainder were not on chronic OCS), and the other focusing on the second component of the reimbursement request (all patients with chronic OCS use). For the combined population, the manufacturer presented three separate analyses that compared benralizumab + SOC individually with SOC alone, mepolizumab + SOC, and omalizumab + SOC. For the population considering chronic OCS patients only, benralizumab + SOC was compared with SOC alone. These analyses were undertaken separately based on an assumption of different baseline characteristics and efficacy inputs (treatment response and exacerbation rate) for each individual comparison.

The following health states were included in the model:

- day-to-day asthma symptoms (receiving biologic treatment)
- day-to-day asthma symptoms (not receiving biologic treatment)
- exacerbation with severity of illness characterized by a) OCS, b) emergency room (ER) visit, or c) hospital admission
- death (Figure 1).

Patients began in one of the “day-to-day symptoms” health states, with a pre-specified proportion of patients expected to be on chronic OCS use, which was defined as receiving 7.5 mg to 40 mg OCS per day for at least six continuous months. Patients receiving biologic treatment moved to the SOC alone upon discontinuation of that treatment due to either non-response, natural attrition, or after maximum treatment duration (10 years). Patients who experienced an exacerbation were in the exacerbation state for four weeks.³

The baseline characteristics and efficacy for each population were determined from pivotal benralizumab trials, and indirect comparisons. A summary of the baseline characteristics and data sources is available in Table 19. The efficacy inputs of primary interest were treatment “response” rates of exacerbation, the proportion of ER visits or hospital admission, and reduction in OCS use (OCS sparing). Different exacerbation rates were used for patients in the benralizumab treatment group based on chronic OCS use and pre-response assessment/responders.

Treatment response for patients not on chronic OCS at baseline was defined as ≥ 50% reduction in annual exacerbation rate or decrease ≥ 0.5 points on the six-question Asthma Control Questionnaire (ACQ-6) or increase of ≥ 0.1 from baseline in the forced expiratory

volume in one second; while for patients on chronic OCS at baseline, response was defined as $\geq 50\%$ OCS dose reduction.³

General population mortality was estimated using Canadian life tables (2012 to 2014) and asthma-related mortality (per cycle) was incorporated from the literature (Watson et al., Roberts et al.) for patients experiencing exacerbations that required an ER visit or hospital admission. Adverse events related to biologic treatment were not included in the model.

Health state utilities were sourced from the trials of benralizumab for different subgroups of patients, and based on Asthma Quality of Life Questionnaire data that were mapped to the EuroQoL 5-Dimensions questionnaire (EQ-5D). Utility values for benralizumab (baseline and responder) and SOC (baseline only) were obtained from the pooled analysis of SIROCCO and CALIMA for patients with no chronic OCS use and ZONDA trial for OCS use. Utility values for SOC at baseline were lower than biologic treatments in both chronic OCS and non-chronic OCS use (■■■■ versus ■■■■, and ■■■■ versus ■■■■). Patients receiving other biologic treatment (mepolizumab or omalizumab) were assumed to have the same day-to-day health state utility values as those receiving benralizumab. Additionally, patients who responded to biologic treatment received an incremental benefit, based on data from the pooled analysis of the CALIMA/SIROCCO studies. Utility decrements for exacerbation states were obtained from literature (Lloyd et al.).⁴ Long-term utility decrements due to adverse events from chronic OCS use were calculated combining data from the ZONDA trial (daily dose), Observational & Pragmatic Research Institute (prevalence on comorbidities), and condition-specific disutility values (diabetes, osteoporosis, glaucoma, cataract, myocardial infarction, peptic ulcer, and pneumonia) from Sullivan et al.⁵

Drug costs of biologic treatments were based on the manufacturer's submitted price and the Ontario Drug Benefit Exceptional Access Program (2017). Administration costs were excluded, assuming that administration would occur in a private clinic at no cost to the public health care payers. SOC (ICS/LABA combination) and OCS costs were obtained from the Ontario Drug Benefit Formulary (2017). Advair received twice daily was assumed to represent SOC. For exacerbation costs, cost of OCS 40 mg for 10 days and 50% cost of clinical consultation was assumed for OCS burst. Costs of clinical consultation, ER visit and asthma hospitalization were obtained from Ontario Schedule of Benefits (2017), Ontario Case Costing Initiative, and Canadian Institute for Health Information. Long-term costs of aforementioned conditions and adverse events (AEs) related to chronic OCS use were derived from Canadian sources.³

Manufacturer's Base Case

The manufacturer reported four base-case analyses:

- I. benralizumab + SOC versus SOC (where 21% of patients require chronic OCS use): \$201,172 per quality-adjusted life-year (QALY) (Table 2)
- II. benralizumab + SOC versus SOC in patients requiring (100%) chronic OCS: \$42,223 per QALY (Table 3)
- III. benralizumab + SOC versus mepolizumab + SOC: \$19,865 per QALY (Table 4).
- IV. benralizumab + SOC versus omalizumab + SOC for \$40,241 per QALY (Table 5).

Table 2: Manufacturer’s Base Case – Combined Population (Case I)

	Benralizumab + SOC	SOC alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	187,132	42,610	144,522
OCS costs	5,004	8,557	-3,553
Exacerbation costs	8,385	10,411	-2,026
Total costs (\$)	200,521	61,577	138,944
Total QALYs	20.515	19.824	0.691
ICUR (\$/QALY)			201,172

OCS = oral corticosteroid; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Manufacturer’s Pharmacoeconomic Report.³

Table 3: Manufacturer’s Base Case – 100% Chronic OCS Use (Case II)

100% OCS use	Benralizumab + SOC	SOC alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	151,701	39,452	112,249
OCS costs	23,452	39,707	-16,255
Exacerbation costs	12,733	19,653	-6,920
Total costs (\$)	187,886	98,813	89,073
Total QALYs	18.183	16.073	2.110
ICUR (\$/QALY)			42,223

OCS = oral corticosteroid; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Manufacturer’s Pharmacoeconomic Report.³

Table 4: Manufacturer’s Base Case – Compared With Mepolizumab (Case III)

	Benralizumab + SOC	Mepolizumab + SOC	Difference (Benralizumab + SOC – Mepolizumab + SOC)
Cost (\$)			
Drug costs	187,480	181,043	6,437
OCS costs	12,284	13,669	-1,385
Exacerbation costs	7,367	8,186	-819
Total costs (\$)	207,132	202,898	4,233
Total QALYs	20.164	19.951	0.203
ICUR (\$/QALY)			19,865

OCS = oral corticosteroid; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Manufacturer’s Pharmacoeconomic Report.³

Table 5: Manufacturer’s Base Case – Compared With Omalizumab (Case IV)

	Benralizumab + SOC	Omalizumab + SOC	Difference (Benralizumab + SOC – Omalizumab + SOC)
Cost (\$)			
Drug costs	187,494	177,893	9,600
OCS costs	5,007	6,938	-1,931
Exacerbation costs	6,938	7,351	-414
Total costs (\$)	199,439	192,183	7,256
Total QALYs	20.725	20.545	0.180
ICUR (\$/QALY)			40,241

OCS = oral corticosteroid; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Manufacturer’s Pharmacoeconomic Report.³

Summary of Manufacturer’s Sensitivity Analyses

Uncertainty was addressed using probabilistic scenario analysis (with discount rates of 0% and 3%). The manufacturer also conducted deterministic scenario analyses that varied model parameters by using alternative values, including: time horizon (base case lifetime versus 10 years); discount rates (1.5% versus 0% and 3%); responder assessment (52 weeks versus 28 weeks or none); annual discontinuation (10% versus 0 or 20%); OCS-related AE costs/utilities (included versus excluded); hospitalization cost (equal between treatments versus length of stay); and SOC costs (Advair versus Symbicort).

Benralizumab + SOC Versus SOC Alone

The base-case deterministic results align with the probabilistic results for the full analysis population. The results were robust except for a time horizon of 10 years: the incremental cost-utility ratio (ICUR) for benralizumab + SOC versus SOC alone is \$430,381 per QALY. The cost-effectiveness acceptability curve from the probabilistic analyses indicated 0% of the ICURs would fall below \$100,000 per QALY.

The base-case deterministic results align with the probabilistic results for the population with 100% chronic OCS use. The results were robust except when considering a shorter time horizon (10 years; \$126,559 per QALY); if duration of biologic therapy was extended to lifetime (\$54,424 per QALY); if no responder assessment was considered (\$60,558 per QALY); if no annual discontinuation rate was considered (\$61,532 per QALY); and when OCS-related AEs were excluded (\$58,223 per QALY). The cost-effectiveness acceptability curve from the probabilistic analyses indicated 72% of the ICURs would fall below \$50,000 per QALY.

Benralizumab + SOC Versus Other Biologics

The base-case deterministic results align with the probabilistic results for both biologics. The results comparing benralizumab + SOC to mepolizumab + SOC were robust except when excluding OCS-related AEs (\$29,266 per QALY). The cost-effectiveness acceptability curve indicated 95% of the ICURs would fall below \$50,000 per QALY.

The results comparing benralizumab + SOC to omalizumab + SOC were robust, except when considering alternate discount rates (0% to 3%; \$27,869 to \$52,894 per QALY); using

a shorter time horizon (10 years; \$174,451 per QALY); assuming increased wastage for omalizumab (benralizumab is dominant); assuming no annual discontinuation (\$52,573 per QALY); and excluding OCS-related AEs: \$62,989 per QALY. According to the cost acceptability curve from the probabilistic analyses, 65% of the ICURs would fall below \$50,000 per QALY.

Limitations of Manufacturer's Submission

- a) **Inappropriate assumptions regarding OCS use.** The manufacturer assumed 21% of patients (in its base case versus SOC) were receiving chronic OCS treatment (defined as 7.5 mg to 40 mg per day for at least six continuous months). The CADTH Common Drug Review (CDR) clinical expert indicated that this was a substantially greater proportion than would be anticipated in Canadian practice. CDR noted that 21% of patients from the pooled CALIMA and SIROCCO trials were on acute OCS treatment, which the manufacturer appeared to assume was equivalent to chronic OCS treatment. The CDR clinical team did not consider this an appropriate assumption. Thus, a lower percentage of chronic OCS use, as estimated by the clinical expert consulted by CDR, was tested in the CDR reanalysis.
- b) **Assumption of increased mortality during exacerbation.** The manufacturer assumed increased mortality when patients had an ER visit or hospital admission. This implies that there is a survival benefit with benralizumab compared with SOC that has not been demonstrated in trials. In addition, the CDR clinical expert commented that asthma-related mortality is preventable if patients are adherent to therapy (including current SOC), and the modelling approach relying on observational data may not reflect what is likely to be observed in adherent patients that have improved control of their asthma. The CDR reanalysis removed this mortality benefit.
- c) **Duration of treatment.** The manufacturer assumed response was assessed at 12 months; patients who did not respond were discontinued, while patients who responded received biologic treatment for up to 10 years. The CDR clinical expert noted that responses were usually assessed at six months. Further, the clinical expert indicated that in real-world practice, biologics (such as omalizumab) are continued to be used past 10 years as long as treatment is funded. Therefore a longer duration on biologic treatment was tested by CDR.
- d) **Treatment response and use in nonresponders.** Response criteria in the trials was defined for patients not on chronic OCS as a $\geq 50\%$ reduction in annual exacerbation rate or decrease (improvement) in ACQ-6 score ≥ 0.5 points from baseline or increase in the forced expiratory volume in one second of ≥ 0.1 L from baseline; and for patients on chronic OCS as a $\geq 50\%$ OCS dose reduction. The model assumed patients not meeting this criterion would no longer take benralizumab. However, it is very likely that a proportion of patients who improve — but not to the extent of the criteria — will continue biologic treatment.
- e) **OCS-related AEs.** Observational data were used to inform the disutility and cost for OCS-related AEs. There is significant uncertainty regarding long-term effects from OCS and if or to what extent benralizumab treatment will reduce them; scenario analyses were performed on these parameters.
- f) **Inappropriate utility value assumptions.** Utility values for the day-to-day health state in the model were derived from different time points of the clinical trials of

benralizumab. The baseline utility values from the benralizumab and SOC groups were considered independently, which favoured benralizumab; and a responder value was attributed to benralizumab that was not attributed to SOC, which also favoured benralizumab. Incorporating a disutility during exacerbation while also considering an increment for response may double-count utility benefits. Furthermore, according to the CDR Clinical Report (Key Efficacy Outcomes), there is no significant difference in EQ-5D visual analogue scale scores between benralizumab and SOC at baseline in both CALIMA and SIROCCO. As such, equal utility values at baseline were assumed in the CDR reanalyses. The assumption of no utility difference between responders and nonresponders, based on chronic OCS use and no chronic OCS use, was also tested in CDR reanalyses.

- g) **Drug administration cost.** The model assumed that treatment administration costs for biologic therapies were excluded from the base case as it was assumed that administration would occur in a private clinic at no cost to the public health care payers. However, there is uncertainty around whether the manufacturer would cover this cost and it is likely that the drug would be administered in a public payer clinic setting; a scenario analysis was performed on this parameter.
- h) **Lack of head-to-head trials among biologics.** The comparison with mepolizumab and omalizumab was based on separate match-adjusted indirect comparisons; there is uncertainty around the relative efficacy of the biologics, and no clear evidence that there is a difference in clinical outcomes (see CDR Clinical Report appendix for details). In addition, different populations were assumed in different comparisons, which made it difficult to interpret the results across different populations.
- i) **No sequential analysis presented.** CDR was unable to consider a single analysis that compared benralizumab against SOC, mepolizumab, and omalizumab, due to the limitations with the indirect comparisons undertaken, and the manufacturer's model structure.

CADTH Common Drug Review Reanalyses

CDR Reanalysis of Benralizumab + SOC Versus SOC Alone

CDR considered the following analyses to address the limitations identified above: The following considerations and reanalyses apply to the comparison of benralizumab + SOC to SOC alone.

1. **Change the proportion of patients on chronic OCS from 21% to between 0% and 5%.** As indicated by the CDR clinical expert, the proportion of patients on chronic OCS use was reduced to examine proportions of 0% to 5%. A value of 5% was used in the CDR base case, as suggested by the clinical expert consulted by CDR.
2. **Assume asthma-related mortality is the same regardless of treatment and exacerbations.** Asthma-related mortality is set to 0.
3. **Duration of treatment.** Increase duration of biologic treatment to 20 years. However, attenuation of treatment effect was not able to be assessed in this analysis.
4. **Change the proportion of nonresponders continued on benralizumab.** In the manufacturer's base case, 0% of nonresponders (which represent ████ of the trial population) were assumed to continue benralizumab at the 12-month assessment. To

simulate possible real-world scenarios, 50% to 100% of nonresponders were assumed to continue on treatment. As the model did not allow nonresponders to stay on benralizumab, an ICUR was manually calculated based on: a) lower attrition rate to simulate increased drug costs, and b) base-case incremental QALYs to simulate no health benefits by continuing on biologic (see Appendix 5).

5. **Assume no disutility and/or cost for OCS-related AEs.** To determine to what extent the model assumes a benefit due to averting long-term AEs from long-term OCS use (which is unproven with current studies), this scenario analysis was conducted.
6. **Assume same utility in the day-to-day health state.** CDR considered the utility for day-to-day asthma should be the same for both treatments (benralizumab + SOC and SOC alone). The utility values for responders were also assumed to be the same as baseline utility values. As such, only utility benefits were obtained from reduced exacerbations.
7. **Assume additional treatment administration cost.** The cost of a general practitioner visit (\$77.20) was added to the treatment administration cost for biologics, as the product monograph for benralizumab indicates benralizumab “should be administered by a qualified health care professional who is experienced in the monitoring of signs and symptoms of hypersensitivity after administration of biologic agents and prepared to manage anaphylaxis that can be life-threatening.”¹
8. **CDR base case.** A plausible CDR base case assume 5% chronic OCS use, same baseline utility in the day-to-day state, and no difference in asthma-related mortality.

In the CDR base-case analysis, assuming 5% chronic OCS use, same utility in the day-to-day health state, and same mortality during exacerbations, the ICUR is > \$1.5 million per QALY compared with SOC alone (Table 6).

Some implications from the scenario analysis:

- The proportion of patients on daily OCS has a significant impact on the results, with less favourable results when a lower proportion of patients are on daily OCS. In a population that consists only of patients on chronic (longer than six months) OCS, the ICUR was approximately \$62,000 per QALY (Table 7).
- Elimination of asthma-related mortality reduces the QALY gains with benralizumab.
- While there is significant uncertainty in the true impact of benralizumab on long-term AEs with OCS, overall it has a relatively minor impact on the base case.
- If nonresponders continue treatment, the ICUR increases further. This may be similar to what would occur if the criteria for nonresponders is less stringent than used in the trials.

Table 6: CDR Reanalysis (Case I – 21% Chronic Oral Corticosteroid use)

	Description	Benralizumab + SOC Compared With SOC Alone		
		Incremental Cost	Incremental QALYs	ICUR (\$/QALY)
	Manufacturer base case	\$138,944	0.691	\$201,172
1	Proportion on chronic OCS			
1a	0%	\$143,622	0.264	\$543,543
1b	5%	\$142,508	0.366	\$389,616
2	Remove asthma-related mortality	\$138,026	0.475	\$290,481
3	Duration of treatment (20 years)	\$177,004	0.790	\$224,142
4	Nonresponders continuing treatment			
4a	50% nonresponders continued treatment (see appendix for calculations)	\$160,019	0.691	\$231,576
4b	100% nonresponders continued treatment	\$185,084	0.691	\$267,849
5	OCS-related AE			
5a	No disutility	\$142,274	0.691	\$205,994
5b	No cost	\$138,944	0.622	\$223,542
5c	No disutility and cost	\$142,274	0.622	\$228,900
6	Same utility in day-to-day state			
6a	Same day-to-day utility regardless of treatment	\$138,944	0.664	\$209,118
6b	Same day-to-day utility regardless of response or treatment	\$138,944	0.529	\$262,463
7	Add treatment administration cost (\$77.20)	\$141,811	0.691	\$205,324
8	CDR base case (1b, 2, 6b)	\$142,553	0.093	\$1,534,803
8a	Scenario analysis of CDR base case with 0% OCS use	\$143,942	0.024	\$6,007,088
8b	Scenario analysis of CDR base case with 50% nonresponders continued treatment	\$163,679	0.093	\$1,759,989
8c	Scenario analysis of CDR base case with incremental quality of life values for responders (0.0384 for chronic OCS use, and 0.0035 for non-OCS use)	\$142,533	0.112	\$1,271,969
8d	Scenario analysis of CDR base case assuming mortality benefit with benralizumab	\$142,508	0.227	\$626,543

AE = adverse event; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCS = oral corticosteroid; QALY = quality-adjusted life-year; SOC = standard of care.

Table 7: CDR Reanalysis (Case II – 100% Oral Corticosteroid Use)

	Description	Benralizumab + SOC Compared With SOC Alone		
		Incremental Cost	Incremental QALYs	ICUR (\$/QALY)
	Manufacturer base case	\$89,073	2.110	\$42,223
1	Proportion on chronic OCS	Not required to be assessed in Case II		
2	Remove asthma-related mortality	\$83,838	1.552	\$54,007
3	Duration of treatment (20 years)	\$115,442	2.241	\$51,512
4	Nonresponders continuing treatment			
4a	25% nonresponders continued treatment (see appendix for calculations)	\$136,742	2.110	\$64,807
5	No OCS-related AE disutility and cost	\$104,264	1.795	\$58,100
6	Same utility in day-to-day state	\$89,073	2.068	\$43,066
6a	Same day-to-day utility regardless of response or treatment	\$89,073	1.905	\$46,754
7	Add treatment administration cost (\$77.20)	\$91,277	2.110	\$43,268
8	CDR base case (1, 6)	\$83,838	1.348	\$62,209
8a	Scenario analysis of CDR base case with 25% nonresponders continued treatment	\$131,437	1.348	\$97,578

AE = adverse event; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OCS = oral corticosteroid; QALY = quality-adjusted life-year; SOC = standard of care.

CDR Reanalysis of Benralizuamb Versus Mepolizuamb or Omalizumab

According to the CDR Clinical Report, the results of the indirect comparison do not clearly show a difference in clinical outcomes between these two agents. A series of scenario analyses were performed. However, given the lack of data that differences exist, it was assumed that the clinical effectiveness and AEs were similar in the CDR base case.

Table 8: CDR Reanalysis – Compared With Mepolizumab (Case III)

	Description	Benralizumab + SOC Compared With Mepolizumab + SOC		
		Incremental Cost	Incremental QALYs	ICUR (\$/QALY)
	Manufacturer base case	\$4,233	0.203	\$19,865
1	5% on chronic OCS	\$4,233	0.203	\$19,865
2	Remove asthma-related mortality	\$3,201	0.114	\$28,016
3	Duration of treatment (20 yrs)	\$4,787	0.241	\$19,841
4	CDR base case Assume same safety and efficacy (cost minimization)	\$5,720	–	Mepolizumab has lower total costs (same QALYs)

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

Table 9: CDR Reanalysis – Compared With Omalizumab (Case IV)

	Description	Benralizumab + SOC Compared With Omalizumab + SOC		
		Incremental Cost	Incremental QALYs	ICUR (\$/QALY)
	Manufacturer base case	\$7,256	0.180	\$40,241
1	5% on chronic OCS	\$8,829	0.070	\$126,419
2	Remove asthma-related mortality	\$6,927	0.148	\$46,805
3	Duration of treatment (20 yrs)	\$8,404	0.182	\$46,084
4	CDR base case Assume same safety and efficacy (cost minimization)	\$9,439	–	Omalizumab has lower total costs (same QALYs)

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

As drug acquisition costs are known, and relative efficacy and safety are unclear, Table 10 presents annual drug acquisition for these agents in the first and subsequent years.

Table 10: Biologic Drug Acquisition Costs

Drug (price per dose \$)	Recommended Dosage	Year 1 Annual Cost (\$)	Subsequent Annual Cost (\$)
Benralizumab (3,876.92)	30 mg every 4 weeks first 3 doses, once every 8 weeks thereafter	31,015	25,200
Mepolizumab (1,938.46)	100 mg every 4 weeks	25,200	25,200
Omalizumab (624 to 1,873)	150 mg to 375 mg every 2 to 4 weeks	24,524 ^a	24,524

^a Assumed to be \$226.69 every two weeks.

Source: Adapted from Manufacturer’s Pharmacoeconomic Report (Table 24).³

A series of price reduction analyses were undertaken based on the CDR base case on benralizumab + SOC versus SOC alone (Table 7), Case I. These indicate that a price reduction of more than 95% may be required to lead to an ICUR < \$50,000 per QALY. For Case II, a price reduction of 15% is required to lead to an ICUR < \$50,000 per QALY.

For comparisons to mepolizumab and omalizumab, assuming same effectiveness and safety, the price of benralizumab would need to be reduced by 4% to 7% (or 1% to 3% with administration costs) to be cost-effective compared with these biologics.

Table 11: CDR Reanalysis Price Reduction Scenarios Based on the CDR Base Case

ICURs of Benralizumab + SOC Versus SOC			
Price	Base-case Analysis Submitted by Manufacturer ICUR (\$/QALY)	Reanalysis by CDR (Case I) ICUR (\$/QALY)	Reanalysis by CDR (Case II) ICUR (\$/QALY)
Submitted	201,172	1,534,803	62,209
25% reduction	149,057	1,145,791	41,640
50% reduction	96,941	756,780	21,341
75% reduction	44,825	367,768	502
90% reduction	13,555	134,361	Dominant (less costly, more effective)
95% reduction	3,133	56,559	Dominant (less costly, more effective)

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

Issues for Consideration

- There may be indication creep with benralizumab used in patients with less-severe asthma patients, as they may prefer less-frequent injection than daily inhalers.
- Another biologic treatment, reslizumab, is currently available in Canada for a slightly different patient population (blood eosinophil count of ≥ 400 cells/ μ L). The manufacturer therefore claimed that an indirect comparison with reslizumab was not feasible due to the high degree of heterogeneity between clinical trials. However, there is likely to be an overlap in the patient population. Due to the lack of comparative clinical information, the cost-effectiveness between benralizumab and reslizumab is unknown.
- It is possible that nonresponders from other biologics might switch to benralizumab, and the clinical expert consulted by CDR suggested that there may be a small portion of patients who would benefit from using a combination of omalizumab and benralizumab, which would increase the drug costs; however, this analysis was not assessed as part of this review.

Patient Input

Patient input was received from six participants in the benralizumab clinical trials (SIROCCO and CALIMA), who viewed benralizumab positively in terms of controlling their asthma symptoms and reducing OCS use. These potential benefits were considered in the economic model (e.g., reduced exacerbation and OCS use).

Conclusions

The primary limitations identified in the review were the lack of comparative clinical information for the population of interest that would allow a sequential analysis and whether the model presented adequately cover the full Health Canada–indicated population.

CDR reanalyses indicated the ICUR for benralizumab + SOC versus SOC alone is likely to be approximately \$1.5 million per QALY. Results were highly sensitive to utility value assumptions, continued usage of biologics for nonresponders, and the proportion of chronic OCS users. When considering only patients with chronic OCS use (six months or more), the ICUR for benralizumab + SOC compared with SOC alone is approximately \$62,000 per QALY. A price reduction of more than 95% is required to achieve an ICUR below \$50,000

per QALY for the reimbursement request population; while a price reduction of 15% is required to achieve an ICUR below \$50,000 per QALY for the population on chronic OCS use.

Benralizumab was more costly and as effective as mepolizumab and omalizumab. A price reduction of 4% to 7% (or 1% to 3% with administration costs) is required for benralizumab to be no more costly than other biologics when considering the combined population.

Appendix 1: Cost Comparison

The comparators presented in Table 12 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. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 12: CDR Cost Comparison Table of Biologics for Eosinophilic Asthma

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price / Dose (\$)	Recommended Dosage	Daily Drug Cost (\$)	Annual Drug Cost (\$)
Benralizumab (Fasenra)	30 mg/mL	Vial of solution for SC injection	3,876.9200^a	3,876.92^a	30 mg every 4 weeks for first 3 doses, then once every 8 weeks^a	84.97	Year 1: 31,015 Year 2 +: 25,200
Biologics							
Mepolizumab (Nucala)	100 mg/mL	Vial of powder for SC injection	1,938.4600 ^b	1,938.46	100 mg every 4 weeks	69.23	25,269
Omalizumab (Xolair)	150 mg	Vial of powder for SC injection	624.2400 ^c	624.24 to 1,872.7 ^d	150 mg to 375 mg is administered SC every 2 or 4 weeks ^e	Low dose: 22.29 High dose: 133.77	Low dose: 8,137 High dose: 48,824
Reslizumab (Cinqair)	10 mg/mL	Vial of solution for IV infusion	640.0000 ^f	640.00 to 2,560.00 ^g	3 mg/kg every 4 weeks	22.86 to 91.43	8,349 to 33,394

CDR = CADTH Common Drug Review; IV = intravenous; SC = subcutaneous.

Note: recommended doses are obtained from product monographs unless otherwise noted.

^a Based on manufacturer's CDR submission for benralizumab.²

^b Price obtained from Delta PA Database.⁶

^c Ontario Drug Benefit Exceptional Access Program (March 2018).

^d Assumes wastage.

^e Dosing is dependent upon body weight and baseline immunoglobulin E, it can range from 150 mg to 300 mg when dosed every four weeks, and 225 mg to 375 mg when dosed every two weeks.

^f Price obtained from CADTH Canadian Drug Expert Committee recommendation for reslizumab.

^g Assumed weight range 30 kg to 120 kg.

Source: Ontario Drug Benefit Comparative Drug Index (effective January 8, 2018) unless otherwise noted.

Table 13: CDR Cost Comparison Table of Other Medications for Asthma

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price/ Dose (\$)	Recommended Dosage	Daily Drug Cost (\$)	Annual Drug Cost (\$)
Inhaled Corticosteroids							
Beclomethasone dipropionate (QVAR)	50 mcg 100 mcg	MDI (200 doses)	32.3500 64.5100	0.1618 0.3226	50 mcg to 400 mcg twice daily	0.32 to 2.58	118 to 942
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	MDPI (200 doses)	31.2700 63.8600 93.0000	0.1564 0.3193 0.4650	200 mcg to 400 mcg twice daily	0.63 to 0.93	228 to 339
Ciclesonide (Alvesco)	100 mcg 200 mcg	MDI (120 doses)	45.5400 75.2800	0.3795 0.6273	100 mcg to 800 mcg twice daily	0.76 to 2.51	277 to 916
Fluticasone furoate (Arnuity Ellipta)	100 mcg 200 mcg	MDPI (30 doses)	38.0500 76.1000	1.2683 2.5367	100 mcg or 200 mcg once daily	1.27 2.54	463 926
Fluticasone propionate (Flovent Diskus)	100 mcg 250 mcg 500 mcg	MDPI (60 doses)	24.3200 41.9580 64.2000	0.4053 0.6993 1.0700	100 mcg to 500 mcg twice daily	0.81 to 2.14	296 to 781
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	MDI (120 doses)	24.3200 ^a 41.9400 83.8920	0.2027 0.3495 0.6991	100 mcg to 500 mcg twice daily	0.81 to 2.80	296 to 1,021
Mometasone furoate (Asmanex Twisthaler)	100 mcg 200 mcg 400 mcg	MDPI (60 doses)	71.3160 ^b 36.3660 72.7440	1.1886 0.6061 1.2124	200 mcg or 400 mcg once daily	2.38 0.61 1.21	868 221 443
ICS/LABA Combinations							
Budesonide/ formoterol fumarate dihydrate (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	MDPI (120 dose pack)	66.8200 86.8300	0.5568 0.7236	One to two inhalations, once to twice daily	0.56 to 2.22 0.72 to 2.89	203 to 813 264 to 1,056
Fluticasone propionate/ salmeterol xinafoate salt (Advair HFA)	125/25 mcg 250/25 mcg	MDI (120 pack)	99.0360 140.5920	0.8253 1.1716	Two inhalations, twice daily	3.30 4.69	1,205 1,711
Fluticasone propionate/ salmeterol xinafoate salt (Advair Diskus)	100/50 mcg 250/50 mcg 500/50 mcg	MDPI (60 doses)	82.7340 99.0360 140.5920	1.3789 1.6506 2.3432	One inhalation, twice daily	2.76 3.30 4.69	1,007 1,205 1,711
Fluticasone furoate/vilanterol (Breo Ellipta)	100/25 mcg 200/25 mcg	MDPI (30 doses)	82.2000 128.7400	2.7400 4.2913	One inhalation, once daily	2.74 4.29	1,000 1,566
Mometasone furoate/formoterol fumarate dihydrate (Zenhale)	50/5 mcg 100/5 mcg 200/5 mcg	MDI (120 doses)	66.3720 ^c 92.2560 111.8160	0.5531 0.7688 0.9318	Two inhalations, twice daily	2.21 3.08 3.73	808 1,122 1,360
Long-Acting Beta2 Agonists (LABA)							
Salmeterol xinafoate (Serevent Diskhaler)	50 mcg	Dry powder inhaler (60 replacement disks) Dry powder inhaler	56.6600	0.9443	50 mcg twice daily	1.89	689

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price/ Dose (\$)	Recommended Dosage	Daily Drug Cost (\$)	Annual Drug Cost (\$)
		(60 doses)	58.7340	0.9789		1.96	715
Formoterol fumarate (Foradil)	12 mcg	Dry powder capsules for inhalation (60 doses)	51.3800	0.8563	12 mcg twice daily	1.71	625
Formoterol fumarate dehydrate (Oxeze Turbuhaler)	6 mcg 12 mcg	MDPI (60 doses)	33.6500 44.8000	0.5608 0.7467	6 mcg to 12 mcg twice daily	1.12 1.49	409 545
Leukotriene Receptor Antagonists (LTRA)							
Montelukast (Singulair, generics)	4 mg 5 mg 10 mg	Chew tab Chew tab Tablet	0.3646 1.2075 1.7735	1.5457 1.7120 2.5044	Age 6 to 14: 5 mg daily Age 15 +: 10 mg daily	1.69 to 2.48	617 to 906
Long-Acting Muscarinic Antagonist (LAMA)							
Tiotropium (Spiriva Respimat)	2.5 mcg	Solution for inhalation (60 doses)	51.9000	0.8650	2 inhalations once daily	1.73	631
Oral corticosteroids							
Prednisone (generic)	1 mg 5 mg 50 mg	Tab	0.1066 0.0220 0.1735	0.0220 to 0.2175	5 mcg to 60 mg daily	0.0220 to 0.2175	8 to 79

CDR = CADTH Common Drug Review; ICS = inhaled corticosteroids; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta2 agonist; LTRA = leukotriene receptor antagonist; MDI = metered dose inhaler; MDPI = multidose-dry powder inhaler; tab = tablet.

Note: Recommended doses are obtained from product monographs unless otherwise noted.

^a Price obtained from Saskatchewan Online Formulary Database.⁹

^b Price obtained from Alberta Online Formulary Database.

^c Price obtained from Delta PA database.⁶

Price source: Ontario Drug Benefit Comparative Drug Index (effective March 7, 2018) unless otherwise noted.⁸

Appendix 2: Summary of Key Outcomes

The following summaries have been provided based on CADTH Common Drug Review reanalyses.

Table 14: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Benralizumab + SOC Relative to SOC Alone (Case I, Case II)?

Benralizumab + SOC vs. SOC alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio	CDR base case: \$1,534,803 per QALY CDR base case (100% OCS use): \$62,209 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; OCS = oral corticosteroid; QALY = quality-adjusted life-year; SOC = standard of care.

Table 15: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Benralizumab + SOC Relative to Mepolizumab + SOC (Case III)?

Benralizumab + SOC vs. Mepolizumab + SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio	CDR base case: Mepolizumab is less costly than benralizumab					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; SOC = standard of care.

Table 16: When Considering Only Costs, Outcomes and Quality Of Life, How Attractive is Benralizumab + SOC Relative to Omalizumab + SOC (Case IV)?

Benralizumab + SOC vs. Omalizumab + SOC	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio	CDR base case: Omalizumab is less costly than benralizumab					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; SOC = standard of care.

Appendix 3: Additional Information

Table 17: 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 18: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR			
<input type="checkbox"/> Adaptation of global model/Canadian model done by the manufacturer <input checked="" type="checkbox"/> Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer <input type="checkbox"/> Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer <input type="checkbox"/> 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 HTA Findings

Benralizumab was recommended for listing on the Section 100 Highly Specialized Drugs Program at the March 2018 meeting of the Pharmaceutical Benefits Advisory Committee (PBAC; Australia) for the treatment of uncontrolled severe eosinophilic asthma in patients aged 12 years and over on the basis of cost minimization compared with mepolizumab. PBAC considered that the estimation of equi-effective doses should include the fixed loading doses of benralizumab, which would be consistent with methods used to estimate the equi-effective doses of other biologics (in other conditions) that require fixed loading doses.¹⁰ No further information on the submission was available at this time.

Benralizumab is currently under review by National Institute for Health and Care Excellence for the treatment of severe asthma; the findings are scheduled to be published in September 2018.¹¹

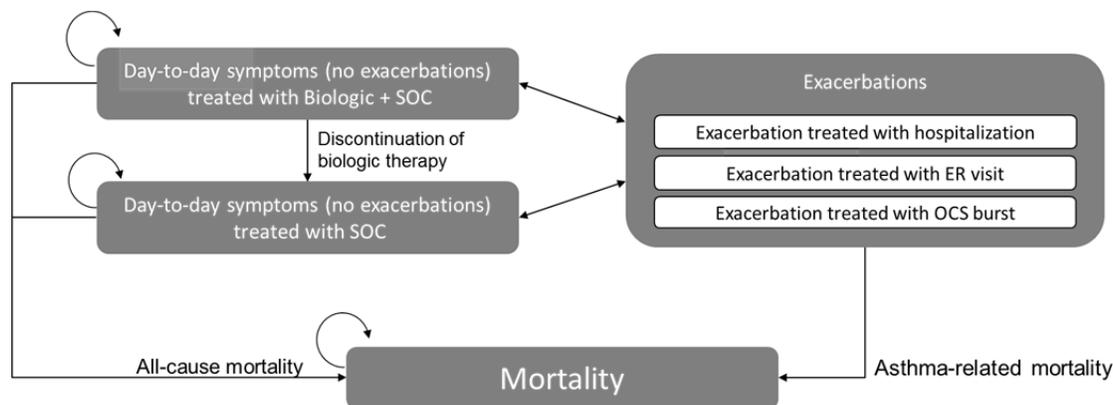
Appendix 5: Reviewer Worksheets

Manufacturer’s Model Structure

A Markov model was developed based on trial data (SIROCCO, CALIMA, and ZONDA) to compare with standard of care, and indirect comparisons (for comparison with mepolizumab and omalizumab).

Details of the Markov structure are shown in Figure 1.

Figure 1: Markov Model Structure



ER = emergency room; OSC = oral corticosteroid; SOC = standard of care.
 Source: Manufacturer’s Pharmacoeconomic Report.³

Health state utilities in the day-to-day symptom state were obtained from subjects in SIROCCO and CALIMA (for those with no chronic oral corticosteroid [OCS] use) or ZONDA (for those with chronic OCS use) by mapping to the EuroQoL 5-Dimensions questionnaire from the Asthma Quality of Life Questionnaire administered to study subjects. Utility decrements for exacerbation states (OCS burst, emergency room visit, and inpatient admission) were obtained from literature.

Patients characteristics in the four manufacturer base-case analyses are listed in Table 19.

Table 19: Patient Characteristics

Input Parameter	BEN + SOC vs. SOC Alone (Pooled SIROCCO/CALIMA; 20.5% OCS)	BEN + SOC vs. SOC Alone (ZONDA; 100% OCS)	BEN + SOC vs. MEPO + SOC (MAIC)	BEN + SOC vs. OMA + SOC (MAIC)
Data Sources	SIROCCO/ CALIMA/ ZONDA	SIROCCO/ CALIMA/ZONDA	SIROCCO/CALIMA/ ZONDA/MAIC	SIROCCO/CALIMA/ ZONDA/MAIC
Mean age, years (SD)	49.9 (12.7)	51.0 (11.3)	49.9 (12.7)	49.9 (12.7)
Proportion of females	63.2%	61.4%	60.8%	65.31%
Proportion of daily maintenance OCS use	20.5%	100%	30.2%	20.1%

BEN = benralizumab; MAIC = matched-adjusted indirect comparison; MEPO = mepolizumab; OMA = omalizumab; OCS = oral corticosteroid; SD = standard deviation; SOC = standard of care.

Note: Pooled refers to patients with a high-dose inhaled corticosteroid + long-acting beta2 antagonist, > 2 exacerbations, blood eosinophil count > 300 cells/μL or OCS. ZONDA refers to patients with maintenance OCS, blood eosinophil count > 150 cells/μL

Source: Manufacturer's Pharmacoeconomic Report.³

Table 20: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Baseline characteristics were informed by the benralizumab registration trials (SIROCCO, CALIMA, and ZONDA). ^{3,12}	Uncertain. The CDR clinical expert indicated that the trial populations may be generalizable to patients likely to receive biologics for patients with severe asthma in the Canadian setting. However, the clinical expert indicated that the model overestimated the proportion of patients on chronic OCS, which is likely much less than 20% (approximately 0 to 5%). The assumption that patient populations would differ between the analyses was highly uncertain and did not allow CDR to test the results sequentially.
Efficacy	Efficacy on exacerbation rate (OCS reactive use, ER visit, hospital admission) and OCS sparing were obtained from a pooled analysis of a subset of patients from the SIROCCO and CALIMA studies, and from the ZONDA trial for benralizumab + SOC vs. SOC alone. Efficacy of benralizumab + SOC vs. other biologics were derived through indirect treatment comparisons (MAIC). ^{3,12,13}	Appropriate, although there is uncertainty in indirect comparisons and limitations with the pooled analysis of SIROCCO and CALIMA. See CDR Clinical Report appendices for details. Data from the long-term BORA study were not incorporated in the economic submission; additional information on this study was provided to CDR after the manufacturer comment period, which may have affected the availability of these data at the time of submission.
Natural history	NA	
Utilities	Health state utilities in the manufacturer's submission were obtained from subjects in the SIROCCO/CALIMA (no chronic OCS) or ZONDA (chronic OCS use, EQ-5D mapped from AQLQ) trials. ^{3,12} Utility decrements for exacerbation states and long-term OCS use (OCS burst, ER visit and inpatient admission) were obtained from literature (Lloyd et al. and Sullivan et al.). ^{4,5}	EQ-5D mapping from AQLQ was based a validated mapping algorithm (Tsuchiya et al.). ¹⁴ Utilities at baseline ("day-to-day symptoms" was lower for SOC (█ to █), which favoured benralizumab; no difference in QoL was noted in the trials The manufacturer also assumed higher utility values for treatment responders for patients receiving a biologic that remained in the day-to-day asthma

Data Input	Description of Data Source	Comment
		state; and a higher utility value for patients not receiving chronic OCS. All studies used to inform were non-Canadian. The duration of disutility was 4 weeks (estimate).
Adverse events	NA	
Mortality	All-cause mortality was estimated using Canadian life tables. Asthma-related mortality from exacerbation was derived from literature and asthma database (Watson et al., Roberts et al., and National Review for Asthma Deaths).	References on asthma-related mortality were all from the UK. The model assumed that reducing exacerbations would reduce asthma-related mortality, based on estimates from observational data. However, this modelling assumption may be flawed; further no mortality benefit has been observed in clinical trials.
Resource use and costs		
Drug (biologic add-on)	Drug costs of biologic were based on the manufacturer's submitted price and the Ontario Drug Benefit Exceptional Access Program. Administration costs were excluded, assuming that administration would occur in a private clinic at no cost to the public health care payers.	Uncertain if manufacturers would cover administration cost. This assumption was tested in the CDR reanalyses.
Drug (SOC: ICS + LABA)	SOC (ICS/LABA combination) costs were obtained from the Ontario Drug Benefit Formulary when the cost of twice-daily Advair was used in the base case.	Appropriate.
Drug (OCS)	OCS costs were obtained from the Ontario Drug Benefit Formulary, while mean daily dose at baseline was based on the ZONDA trial (14.28 mg).	Appropriate.
Administration	NA	
Event (Exacerbation)	For exacerbation costs, cost of OCS 40 mg for 10 days and 50% cost of clinical consultation was assumed for OCS burst. Costs on clinical consultation, ER visit and asthma hospitalization were obtained from Ontario Schedule of Benefits, Ontario Case Costing Initiative, and CIHI.	Appropriate.
OCS-related AEs	Long-term costs of conditions and AEs related to chronic OCS use were derived from Canadian sources.	Appropriate, but might overestimate costs as not some conditions do not develop in the short-term. Also, significant uncertainty exists in the true reduction of these events.

AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; EQ-5D = EuroQoL 5-Dimensions questionnaire; ER = emergency room; ICS = inhaled corticosteroid; LABA = long-acting beta2 antagonist; MAIC = matched-adjusted indirect comparison; NA = not applicable; OSC = oral corticosteroid; QoL = quality of life; SOC = standard of care.

Table 21: Manufacturer’s Key Assumptions

Assumption	Comment
The patients’ characteristics from the trials were assumed to be representative to the target population. Different patient populations were also assumed for different comparisons.	The CDR clinical expert noted that the although the trial populations were similar to the populations in whom biologic treatments will be used in the Canadian population, the manufacturers assumption that 20% to 30% of patients were on chronic OCS use is a large overestimation of chronic OCS use in Canadian practice (0% to 5%); and a misrepresentation of the data, as the CALIMA and SIROCCO trials noted OCS use at baseline, but not the well-defined chronic OCS use that the manufacturer specified for ZONDA.
Efficacy was assumed to remain constant beyond the study follow-up time.	Uncertain. Feedback from the CDR clinical expert suggested biologic efficacy may reduce over time.
Non-Canadian utilities and decrements were used in the model.	Uncertain. May not represent the Canadian patients’ population quality of life, but reasonable approach. However, the assumption regarding different baseline and day-to-day asthma health state utility values for patients based on treatment is inappropriate, and the responder increment for patients receiving biologics only biases the results in favour of patients receiving these drugs.
Observational data on asthma mortality with exacerbation implies reduction in exacerbation leads to a survival benefit.	Asthma or all-cause survival has not been shown to be improved in available trials. Further, the clinical expert indicates that mortality due to asthma in adherent patients is very low; observational data that reports on mortality by exacerbation is unlikely to account for this.
Maximum duration of treatment with a biologic is 10 years, consistent with mepolizumab and reslizumab.	Uncertain. It has been observed in clinical practice that some patients have used omalizumab for more than 10 years.
The rate of annual treatment discontinuation was assumed to be 10% for biologic therapies.	Uncertain. The CDR clinical expert commented about patients preferred less-frequent biologic therapies than daily inhalers.
Patients on biologics were assessed for response to therapy at 52 weeks based on clinician-validated response criteria; those that do not respond would be discontinued.	Uncertain. The CDR clinical expert indicated that response would usually be assessed at 26 weeks. In clinical practice it is likely that many patients would remain on benralizumab despite not meeting all response criteria.

CDR = CADTH Common Drug Review; OSC = oral corticosteroid.

CDR Reanalyses

As the model did not allow nonresponders to stay on benralizumab, CADTH Common Drug Review (CDR) had to undertake individual calculations. The proportion of nonresponders from the pooled analysis of SIROCCO and CALIMA was [REDACTED]. In the CDR reanalyses, we assumed 50% of nonresponders ([REDACTED] of the model cohort) continuing benralizumab without any clinical benefits. First, to estimate the increased treatment cost, lower attrition rate ([REDACTED] instead of [REDACTED], resulting [REDACTED] additional patients on treatment) was used in the model. The new treatment cost from the lower attrition rate was used to calculate the new incremental cost-utility ratio by dividing it using the incremental quality-adjusted life-years from the base case (assuming no health benefits on those [REDACTED] patients). Similarly, to derive the treatment cost for 100% of nonresponders ([REDACTED] of the model cohort) continuing benralizumab, the attrition rate was lowered from [REDACTED] to [REDACTED] (resulting additional [REDACTED] patients).

Table 22: CDR Reanalyses – Case I (Analysis 4a)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC Alone)
Cost (\$)			
Drug costs	208,207	42,610	165,597
OCS costs	5,004	8,557	-3,553
Exacerbation costs	8,385	10,411	-2,026
Total costs (\$)	221,596	61,577	160,019
Total QALYs	20.515	19.824	0.691
ICUR (\$/QALY)			231,576

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

Increased drug cost was derived from decreasing attrition rate from █████ to █████.

Table 23: CDR Reanalyses – Case I (Analysis 4b)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	233,272	42,610	190,662
OCS costs	5,004	8,557	-3,553
Exacerbation costs	8,385	10,411	-2,026
Total costs (\$)	246,661	61,577	185,084
Total QALYs	20.515	19.824	0.691
ICUR (\$/QALY)			267,849

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

Increased drug cost was derived from decreasing attrition rate from █████ to █████.

Table 24: CDR Reanalysis – Case I (Analysis 8)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	189,817	45,310	144,507
OCS cost	1,323	2,311	-988
Exacerbation costs	7,976	8,961	-985
Total costs (\$)	199,116	56,582	142,533
Total QALYs	21.650	21.557	0.093
ICUR (\$/QALY)			1,534,803

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

Table 25: CDR Reanalysis – Case I (Analysis 8b)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	210,962	45,310	165,652
OCS cost	1,323	2,311	-988
Exacerbation costs	7,976	8,961	-985
Total costs (\$)	220,261	56,582	163,679
Total QALYs	21.650	21.557	0.093
ICUR (\$/QALY)			1,759,989

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

Increased drug cost was derived from decreasing attrition rate from █████ to █████.

Table 26: CDR Reanalysis – Case II (Analysis 4a)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	199,370	39,452	159,918
OCS cost	23,452	39,707	-16,255
Exacerbation costs	12,733	19,653	-6,920
Total costs (\$)	235,555	98,813	136,742
Total QALYs	18.183	16.073	2.110
ICUR (\$/QALY)			64,807

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

Increased drug cost was derived from decreasing attrition rate from █████ to █████.

Table 27: CDR Reanalysis – Case II (Analysis 8a)

	Benralizumab + SOC	SOC Alone	Difference (Benralizumab + SOC – SOC alone)
Cost (\$)			
Drug costs	202,668	44,189	158,479
OCS cost	26,159	45,097	-18,938
Exacerbation costs	14,235	22,339	-8,104
Total costs (\$)	243,062	111,625	136,742
Total QALYs	19.289	17.942	1.347
ICUR (\$/QALY)			97,578

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

Increased drug cost was derived from decreasing attrition rate from █████ to █████.

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