Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	mepolizumab (Nucala)
Indication	For the add-on maintenance treatment of adult patients with severe eosinophilic asthma who: – are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA), and – have a blood eosinophil count of ≥ 150 cells/mcL (0.15 GI/L) at initiation of treatment with mepolizumab OR ≥ 300 cells/mcL (0.3 GI/L) in the past 12 months.
Reimbursement request	For the treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s), and who have either experienced ≥ 2 exacerbations in the past 12 months or have dependency on systemic corticosteroids.
Dosage form(s)	Lyophilized powder for subcutaneous injection, 100 mg/mL
NOC date	3 December 2015
Manufacturer	GlaxoSmithKline Inc.

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 respiratory diseases who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides drug reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ARM	asthma-related mortality
CDR	CADTH Common Drug Review
EQ-5D	EuroQoL 5-Dimensions questionnaire
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
OCS	oral corticosteroid
QALY	quality-adjusted life-year
SGRQ	St. George's Respiratory Questionnaire
SOC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Mepolizumab (Nucala) 100 mg SC injection
Study Question	• What is the estimated ICER (in terms of QALYs and exacerbations avoided) of mepolizumab therapy compared to current standard of care (SOC) for the treatment of severe eosinophilic asthma over a lifetime time horizon?
Type of Economic Evaluation	• CUA • CEA
Target Population	Patients with severe eosinophilic asthma
Treatment	Mepolizumab 100 mg SC injection once every 28 days in addition to SOC
Outcomes	• QALYs • Exacerbations avoided
Comparators	• SOC (high-dose ICS + additional controller medication [e.g., LABA, LTRA, theophylline], with or without systemic OCS) • Omalizumab was considered as a comparator for patients with severe eosinophilic asthma who have allergic asthma
Perspective	Canadian health care system perspective
Time Horizon	Lifetime
Results for Base Case	Compared with SOC: • ICUR: $143,778 per QALY gained • ICER: $22,540 per exacerbation avoided Compared with omalizumab: • Mepolizumab is associated with more QALYs and fewer costs than (i.e., dominates) omalizumab
Key Limitations	• Uncertainty in the utility values used • Use and quality of the comparative clinical data, modelling of age, and dosing of omalizumab
CDR Estimates	CDR tested various assumptions for the following parameters: utility values, age at model entry, time horizon, dose of omalizumab, use of comparative clinical evidence, and duration of biologic treatment: • MEP + SOC vs. SOC alone: ICER ranged from $138,000 per QALY to $243,000 per QALY. The driver of the difference in ICERs was the choice of utility values used. • If MEP + SOC is assumed to be as effective as OMA + SOC, it is cost-saving based on treatment cost and utilization assumptions. There is uncertainty regarding the comparative efficacy and safety of mepolizumab compared with omalizumab. Omalizumab is reimbursed through special access schemes by a few jurisdictions. CDR's base case simultaneously addressed identified limitations, including the use of directly derived utility values, a reduced time horizon to account for uncertainty in the way age was modelled, consistent sources of data for the comparison of MEP + SOC vs. SOC alone, assumption of equal efficacy for mepolizumab and omalizumab, and reduced omalizumab vial use. • MEP + SOC vs. SOC alone: ICER = $521,000. In jurisdictions that do not reimburse omalizumab, mepolizumab would require a price reduction of 80% to 89% to be considered cost-effective at willingness-to-pay thresholds of $100,000 per QALY

	and $50,000 per QALY respectively. • MEP + SOC vs. OMA + SOC: Over the CDR time horizon, mepolizumab resulted in a cost-saving of $[redacted] compared with omalizumab (based on treatment cost only); however, the comparative efficacy and safety of mepolizumab versus omalizumab is associated with substantial uncertainty.

CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroids; ICUR = incremental cost-utility ratio; LABA = long-acting beta$_2$ agonist; LTRA = leukotriene receptor antagonist; MEP = mepolizumab; OCS = oral corticosteroid; OMA = omalizumab; QALY = quality-adjusted life-year; SC = subcutaneous; SOC = standard of care; vs. = versus.

EXECUTIVE SUMMARY

Background

Mepolizumab (Nucala), a fully humanized immunoglobulin G (IgG) monoclonal antibody specific for interleukin-5, is available as a 100 mg/mL vial of lyophilized powder for subcutaneous injection for add-on maintenance treatment to standard of care (SOC) for adult patients with severe eosinophilic asthma.[1] SOC was defined as high-dose inhaled corticosteroid and additional controller medication (e.g., long-acting beta agonist, leukotriene receptor antagonist, or theophylline), with or without maintenance oral corticosteroid. The manufacturer considered omalizumab — a biologic therapy for the treatment of moderate to severe allergic asthma — as an appropriate comparator in a small subset of patients with features of both severe eosinophilic and allergic asthma.[1] At the time of the mepolizumab review, the CADTH Common Drug Review (CDR) was reviewing omalizumab for moderate to severe asthma. In 2006, the CADTH Canadian Expert Drug Advisory Committee (CEDAC) recommended that omalizumab not be reimbursed for this indication.[2] The manufacturer submitted mepolizumab at a confidential unit price of $[redacted] per vial.[1]

The manufacturer's primary evaluation was a cost-effectiveness analysis of mepolizumab plus SOC compared with SOC alone that reported incremental cost per quality-adjusted life-years (QALYs) and cost per exacerbation avoided. The incremental cost-effectiveness ratio (ICER) was approximately $143,000 per QALY and $22,540 per exacerbation avoided. The manufacturer reported that at a willingness-to-pay threshold of $100,000 per QALY, there is a < 1% likelihood that mepolizumab plus SOC is cost-effective. The manufacturer presented an additional analysis comparing mepolizumab plus SOC to omalizumab plus SOC, concluding that mepolizumab plus SOC was associated with a cost-saving of $65,192 and greater benefits with respect to both QALYs and exacerbations avoided compared with omalizumab plus SOC; that is, mepolizumab plus SOC is dominant.[1]

Summary of Identified Limitations and Key Results

CDR identified several limitations with the manufacturer's pharmacoeconomic submission, including:

- Cost-effectiveness results varied considerably with changes in age at model entry, and it was observed that the manufacturer's base-case analysis was based on a value for age at model entry that resulted in nearly the lowest possible incremental cost-utility ratio. The model predicted a higher ICER than the base case when either a younger (< 45 years) or older (> 50 years) age at model entry was used. This pattern was due to large differences across age bands in asthma-related mortality (ARM) rates (in particular the much higher ARM risk in patients ≥ 45 years compared with younger age bands, and the lack of disaggregated ARM data within this age band for elderly patients, who likely have the highest ARM rates). An analysis using a weighted average of patient ages reflective of the Canadian population likely to be treated with mepolizumab may have been more appropriate than use of a single value for age at model entry. It was noted that the difference in ICERs according to age was attenuated over a shorter time horizon (i.e., 10 years).
- The manufacturer's model predicts a mortality benefit of mepolizumab over SOC at 10 years, the time point at which mepolizumab is assumed to be discontinued. After treatment discontinuation, both groups have the same probabilities for asthma-related outcomes. CDR noted that, unlike the QALY results at 10 years, which are driven by both life-years gained and quality-of-life gains, incremental QALYs accrued with mepolizumab over SOC from the point of treatment discontinuation until death are due almost entirely to additional life-years resulting from the difference in 10-year mortality. In the absence of clinical data demonstrating a mortality benefit with mepolizumab, this is an important

source of uncertainty in the cost-effectiveness results; particularly over a lifetime time horizon as these results rely more heavily on the predicted reduction in mortality.
- The manufacturer used a mapping algorithm to determine health-state utility values, rather than using directly measured utility values that were collected in one of the mepolizumab trials. The model results are sensitive to the utility values used; directly measured utility values are preferred in the base-case analysis, though the sensitivity of the results may be tested using other measures.
- The manufacturer may have overestimated the average dose of omalizumab based on a CDR review of utilization data; reducing the average dose of omalizumab would reduce the apparent cost-effectiveness of mepolizumab compared with omalizumab.
- The CDR clinical reviewers were unable to form conclusions regarding the comparative efficacy and safety of mepolizumab and omalizumab based on serious limitations in the available indirect treatment comparisons (ITCs). CDR undertook analyses testing an assumption of equivalent efficacy.
- The manufacturer used efficacy inputs from the direct head-to-head trial for SOC, but used efficacy inputs from the ITC for mepolizumab plus SOC. This is not appropriate; data from a single source (head-to-head study or ITC) should have been used.

One-way CDR reanalyses to address some of these limitations (i.e., use of directly measured utility values, reduced time horizon of 10 years, consistent use of trial-based clinical inputs for both mepolizumab plus SOC and SOC, assumption of equal efficacy for omalizumab and mepolizumab, omalizumab utilization based on claims data) resulted in an incremental cost-utility ratio ranging from $138,000 per QALY to $243,000 per QALY for mepolizumab plus SOC versus SOC alone. For the comparison of omalizumab with mepolizumab, CDR reanalyses suggested that mepolizumab is less costly than omalizumab (when more than [redacted] vials of omalizumab are used per administration).

For the CDR base case, a multi-way reanalysis was conducted that incorporated the revised inputs from the one-way reanalyses. The resulting ICER for mepolizumab plus SOC versus SOC alone was $521,000 per QALY. For the population eligible for either omalizumab or mepolizumab, mepolizumab is less costly based on CDR assumptions, resulting in a drug cost-saving of $[redacted]. However, the comparative efficacy and safety are unknown. In jurisdictions that do not reimburse omalizumab for patients with severe eosinophilic asthma requiring add-on treatment, a price reduction of 80% to 89% for mepolizumab would be required to achieve willingness-to-pay thresholds of $100,000 per QALY and $50,000 per QALY respectively. In jurisdictions that reimburse omalizumab for this patient population, mepolizumab appears to be less costly than omalizumab based on the publically listed price of omalizumab.

Conclusions

The results of the pharmacoeconomic analyses undertaken both by CDR and the manufacturer indicated that mepolizumab as an add-on to SOC for adult patients with severe eosinophilic asthma was not cost-effective, at conventionally accepted thresholds, compared with SOC alone. The CDR base-case analysis, addressing some of the identified limitations, resulted in an ICER of $521,000 per QALY. A price reduction for mepolizumab of 89% is required to obtain an incremental cost-utility ratio of $50,000 per QALY or a price reduction of 80% to obtain an incremental cost-utility ratio of $100,000 per QALY. For jurisdictions that reimburse omalizumab for patients with severe eosinophilic asthma requiring add-on treatment, mepolizumab may be cost-saving compared with omalizumab (at up to [redacted] vials per administration of the latter), but the comparative clinical efficacy and safety of mepolizumab versus omalizumab is uncertain; thus, a conclusion regarding the cost-effectiveness in this comparison cannot be made.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer undertook a cost-utility analysis to capture all costs and quality-adjusted life-years (QALYs) over the lifetime of the expected patient cohort with severe eosinophilic asthma and to capture all relevant clinical and economic parameters related to the therapies. This analysis was undertaken based on the claim of superior efficacy of mepolizumab in addition to standard of care (SOC) compared with SOC alone in terms of reduced exacerbations and reduced oral corticosteroid (OCS) use. The manufacturer also undertook an analysis comparing mepolizumab plus SOC with omalizumab plus SOC.

The manufacturer submitted a Markov health-state transition model that used published and unpublished clinical data from the DREAM,[1,3] MENSA,[1,4,5] and SIRIUS[1,6,7] trials to compare mepolizumab plus SOC with SOC alone and data from an indirect comparison[8] to inform the comparison of mepolizumab plus SOC to omalizumab plus SOC. The model followed a hypothetical cohort of patients with baseline characteristics from the MENSA trial[4,5] over a lifetime duration. The model cycle length was 28 days (per mepolizumab administration schedule).[1,9] Patients in the mepolizumab and omalizumab groups received these treatments for up to 10 years, at which point all patients received treatment with SOC alone. The model included health states based on day-to-day asthma symptoms, asthma-related and all-cause mortality, and three categories of exacerbation events (short-term OCS use, emergency department visits, and hospitalizations). From the day-to-day asthma symptom health states, patients were at risk of an exacerbation or death in each model cycle. The effect of long-term OCS use was assessed in a scenario analysis. Although EuroQoL 5-Dimensions questionnaire (EQ-5D) values were collected directly from the DREAM trial, the utility values used in the model were derived from the mapping of St. George's Respiratory Questionnaire (SGRQ) scores from the MENSA trial to the EQ-5D (unpublished data).[1] Direct medical costs included drug treatments, disease monitoring, and in-patient and outpatient costs relating to exacerbations. Unit costs were derived from the manufacturer[1] and Canadian sources[10-16] based on the recommended doses and available pack sizes specified in the product monographs. Costs and effects accrued beyond one year were discounted at 5%. The manufacturer's deterministic analysis of mepolizumab plus SOC versus SOC alone was undertaken using inputs for mepolizumab plus SOC derived from the indirect treatment comparison (ITC), while data from the MENSA trial were used to inform the SOC-alone group.

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case deterministic analysis observed that the incremental cost of mepolizumab plus SOC versus SOC alone was $124,842, with an incremental QALY gain of 0.868 and 5.54 exacerbations avoided. The resulting deterministic incremental cost-effectiveness ratios (ICERs) were $143,778 per QALY gained and $22,540 per exacerbation avoided. When mepolizumab plus SOC was compared with omalizumab plus SOC, the manufacturer reported a cost-saving of $65,192 with mepolizumab, a QALY gain of 0.226, and 2.70 exacerbations avoided; thus, mepolizumab plus SOC dominated omalizumab plus SOC as it was less costly with greater benefits.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer's sensitivity analyses observed that the model was sensitive to changes in the relative risk of exacerbations and the source of the utility inputs; the ICER for mepolizumab plus SOC versus SOC alone ranged from $115,000 per QALY to $189,000 per QALY. In all the parameters varied in the analysis of mepolizumab plus SOC versus omalizumab plus SOC, mepolizumab plus SOC remained dominant (i.e., less costly with more QALYs; the ICER ranged from –$195,000 to –$747,000 per QALY).

The manufacturer reported that a multivariate probabilistic sensitivity analysis with 2,000 simulations generated ICERs similar to the deterministic results ($143,162 per QALY for mepolizumab plus SOC versus SOC alone), and mepolizumab plus SOC continued to dominate omalizumab plus SOC. The cost-effectiveness acceptability curve showed that at a willingness-to-pay of $50,000, the probability of mepolizumab plus SOC being cost-effective compared with SOC alone was 0%. At a willingness-to-pay of $100,000, the probability that mepolizumab plus SOC is cost-effective was < 1%.

The manufacturer indicated that scenario analyses were undertaken to test the impact of changes to key structural and data assumptions on the ICERs. Use of EQ-5D values from DREAM rather than mapped values, a shorter time horizon (one year), and reducing the baseline age of patients from 50 years to 30 years all substantially increased the ICER to between $217,000 and $245,000 per QALY. An abbreviated treatment duration (one year, five years) and lack of discounting reduced the ICER, though not below $100,000 per QALY. When OCS and associated adverse effects were included in a scenario analysis, the ICER remained at approximately $143,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The CADTH Common Drug Review (CDR) identified the following limitations with the manufacturer's pharmacoeconomic submission:

- *Inconsistent results based on age at model entry:* The age at model entry was tested by the manufacturer in one-way sensitivity analyses; 30 years and 65 years were the ages tested. This analysis demonstrated an inconsistent trend in the ICERs, with the highest ICER at the minimum age modelled (30 years), the lowest ICER at the manufacturer's base-case value (50.1 years), and an ICER at 65 years of age that was higher than at 50.1 years (although not to the level observed at 30 years). CDR undertook further analyses with smaller increments, which indicated that the ICER decreased with increasing age between 30 and 45 years and then increased with every additional year up to the maximum age tested by CDR (70 years). This pattern appears to be a result of the source data for asthma-related mortality (ARM), which indicated that the ARM rate was lower for patients 17 to 44 years of age (0.38%) compared with the ≥ 45 years age group (2.48%). [17] Although the inconsistent results appear to reflect limitations with the source data (i.e., the lack of disaggregated data for elderly patients, who are likely to have the highest ARM rates), CDR noted that the age at model entry selected by the manufacturer results in nearly the lowest possible ICER. A related issue is that the age at entry may have been overestimated in the manufacturer's model (i.e., the patient population in Canadian practice treated with mepolizumab may be younger on average), based on input from the clinical expert consulted by CDR. In light of the limitations associated with using a single age at model entry, a more appropriate approach to the analysis would have been one that weighted the results based on an age distribution reflective of Canadian patients likely to be treated with mepolizumab.

- *Uncertainty regarding mortality benefits:* The manufacturer's model predicts a mortality benefit of mepolizumab over SOC at 10 years, the time point at which mepolizumab is assumed to be discontinued (i.e., 8.1% and 12.6% mortality in the mepolizumab and SOC groups, respectively). After treatment discontinuation, both groups have the same probabilities for asthma-related outcomes. CDR noted that, unlike the QALY results at 10 years which are driven by both life-years gained and quality-of-life gains, incremental QALYs accrued with mepolizumab over SOC from the point of treatment discontinuation until death are due almost entirely to additional life-years resulting from the difference in 10-year mortality. In the absence of clinical data demonstrating a mortality benefit with mepolizumab, the long-term benefits of treatment on mortality remain uncertain. Therefore, this is an important source of uncertainty in the cost-effectiveness results, particularly over a lifetime time horizon, as these results rely more heavily on the predicted reduction in mortality.
- *Use of mapped health-state utility values:* Utility values for the day-to-day asthma symptom states were derived indirectly from SGRQ data using a mapping technique not validated in this patient population. Utility values were captured directly in the DREAM trial but used only in a sensitivity analysis rather than the base-case analysis as they were considered to overestimate the baseline health status of patients with severe eosinophilic asthma, and the EQ-5D was thought to have insufficient sensitivity for changes in asthma symptoms. Despite these potential limitations, the use of directly measured utility values from the DREAM trial in the base-case analysis would have been preferred to mapped values from a different clinical population.
- *Inconsistency in utility value estimation procedures*: Although the manufacturer used health-state utility values based on mapped values, they used a source reporting directly derived values for the disutilities due to exacerbation. Given the manufacturer's argument that mapped values are appropriate, the rationale for using directly derived values when other values based on mapping procedures are available was not appropriately justified.[18,19] As noted in the first bullet point, direct values are preferred to mapped values.
- *Dose of omalizumab:* The assumed dose of omalizumab in the model impacts the comparative costs of mepolizumab and omalizumab. The manufacturer's assumption of 3.15 vials per 28-day cycle appears to be an overestimate based on a CDR review of IMS Brogan data (which indicates 2.32 to 2.35 vials per claim) and feedback from the CDR clinical expert indicating an average dose of 300 mg every four weeks; i.e., two vials per 28-day cycle. Overestimation of omalizumab utilization would tend to improve the apparent cost-effectiveness of mepolizumab.
- *Choice of clinical evidence (use of data from ITC versus randomized controlled trial):* The manufacturer's analysis of mepolizumab plus SOC compared with SOC alone uses data from the head-to-head trial for SOC and data from the ITC for mepolizumab plus SOC. The use of two separate data sources was not justified and is not considered appropriate.
- *Uncertainty regarding the comparative effectiveness of omalizumab and mepolizumab:* The CDR clinical review of the manufacturer's ITC found that there were substantial limitations with the ITC, including [redacted], CDR reviewers observed that these findings should be interpreted with caution. Due to the identified limitations of the analysis, CDR

clinical reviewers could not make any conclusions regarding the comparative efficacy and safety of mepolizumab versus omalizumab in the patient population currently under review.

- *Duration of biologic treatment:* There is no adequate published evidence regarding long-term use of biologic treatment in asthma patients. The CDR clinical expert indicated that asthma is a chronic disease, and if the patient maintains response while on the biologic, and in the absence of safety signals, it was reasonable to assume patients could receive biologic treatment indefinitely. However, the lack of long-term data means that there is uncertainty about whether the efficacy and safety profiles observed in short-term trials are maintained over the long term.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook a series of one-way analyses based on the limitations identified above:

- *Revised time horizon:* Given the inconsistency in ICERs across different ages at model entry, CDR undertook an analysis to shorten the time horizon to 10 years, in line with the duration of biologic therapy. This was done with the expectation that a reduced time horizon would attenuate the anomalous differences in ICERs between the manufacturer's base case and the lower and higher ends of the age range. Although somewhat simplistic, a 10-year time horizon may also be appropriate under the assumption that beyond this time point, costs and QALYs would be the same for both groups once mepolizumab is discontinued and all patients receive SOC. This revision resulted in an increased ICER for mepolizumab plus SOC compared with SOC alone of $200,000 per QALY.
- *Utility values:* Use of directly derived utility values from the DREAM study substantially increased the ICER when mepolizumab plus SOC was compared with SOC alone ($243,000 per QALY, as reported in the manufacturer's scenario analysis). Use of other mapped values reported in the literature[18,19] resulted in ICERs that were lower ($138,000 per QALY) and higher ($179,000 per QALY) than the manufacturer's base case.
- *Omalizumab dose:* Use of the average number of omalizumab vials from CDR's review of Pharmastat data (i.e., 2.35 vials per claim) reduced the incremental savings associated with mepolizumab, although mepolizumab plus SOC continued to dominate omalizumab plus SOC. Feedback from the clinical expert consulted by CDR suggested that the usual dose of omalizumab was 300 mg every 4 weeks (i.e., two vials); [redacted]. The threshold number of omalizumab vials per 28-day cycle at which mepolizumab plus SOC no longer dominates omalizumab plus SOC (assuming the manufacturer's other base-case assumptions hold) is [redacted].
- *Duration of biologic:* CDR noted that the ICERs were sensitive to the assumed duration of biologic treatment, such that they increased slightly as the duration of biologic treatment increased (e.g., from one year to lifetime, Table 13). However, as there is no reliable estimate or assumption around the average duration of biologic treatment, and a duration of 10 years has been used in other health technology assessments (HTAs) for a similar patient population (i.e., severe persistent allergic asthma), CDR did not revise the base-case treatment duration in the multi-way analysis.
- *Source of comparative data for mepolizumab versus SOC:* CDR undertook reanalyses using direct trial evidence (from MENSA) for both mepolizumab plus SOC and SOC alone. This resulted in a slightly increased ICER of $146,000 per QALY.
- *Comparative efficacy of mepolizumab versus* omalizumab: Under an assumption of no difference in comparative efficacy for omalizumab plus SOC compared with mepolizumab plus SOC (i.e., a QALY difference of 0), mepolizumab plus SOC was cost-saving compared with omalizumab plus SOC ($[redacted] over the lifetime time horizon).

CDR undertook a multi-way analysis assessing the impact of age at entry and a time horizon of 10 years. The results indicated that the anomalous differences observed at the lower and higher ends of the age range were reduced, but not entirely eliminated, with the shortened time horizon (Table 15).

The CDR base-case scenario analysis simultaneously addressed the identified areas of uncertainty and limitations that could be addressed in the model (i.e., use of directly measured utility values, reduced time horizon of 10 years to address anomalous results associated with age at model entry, consistent use of trial-based clinical inputs for both mepolizumab plus SOC and SOC, assumption of equal efficacy for omalizumab and mepolizumab, and omalizumab utilization based on claims data). The ICER from this multi-way reanalysis for mepolizumab plus SOC versus SOC alone was $521,000 per QALY. For the population eligible for either omalizumab or mepolizumab, where omalizumab is available for this indication, CDR was unable to determine the comparative efficacy and safety for mepolizumab compared with omalizumab; however, based on drug costs alone, mepolizumab resulted in cost-savings of $[redacted] over the 10-year time horizon. Given the lack of appropriate comparative efficacy and safety data for mepolizumab versus omalizumab, no determination around cost-effectiveness can be made.

CDR undertook price reduction scenario analyses based on the manufacturer's base-case cost-utility analysis and CDR's base-case cost-utility analysis (Table 2).

TABLE 2: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS FOR MEPOLIZUMAB PLUS STANDARD OF CARE COMPARED WITH STANDARD OF CARE ALONE

ICERs for MEP + SOC Compared With SOC Alone		
Price	**Base-Case Analysis Submitted by Manufacturer**	**CDR Base Case**
Submitted ($[redacted])	$143,778 per QALY	$521,838 per QALY
10% reduction ($[redacted])	$129,251 per QALY	$468,729 per QALY
20% reduction ($[redacted])	$114,725 per QALY	$415,621 per QALY
30% reduction ($[redacted])	$100,198 per QALY	$362,513 per QALY
40% reduction ($[redacted])	$85,671 per QALY	$309,404 per QALY
50% reduction ($[redacted])	$71,144 per QALY	$256,296 per QALY
60% reduction ($[redacted])	$56,617 per QALY	$203,188 per QALY
65% reduction ($[redacted])	$49,354 per QALY	$176,633 per QALY
70% reduction ($[redacted])	$42,091 per QALY	$150,079 per QALY
80% reduction ($[redacted])	$27,564 per QALY	$96,971 per QALY
90% reduction ($[redacted])	$13,037 per QALY	$43,862 per QALY

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; MEP = mepolizumab; QALY = quality-adjusted life-year; SOC = standard of care.

The ICER for mepolizumab plus SOC compared with SOC alone would fall below $100,000 per QALY based on the CDR base-case analysis if the price of mepolizumab was reduced by approximately 80%, while a price reduction of approximately 89% would be required for the ICER to fall below $50,000 per QALY.

6. ISSUES FOR CONSIDERATION

- Omalizumab may not be a direct comparator for mepolizumab for all patients with severe eosinophilic asthma. The clinical expert consulted by CDR noted that while some patients will be eligible for either treatment, in practice patients with a higher immunoglobulin E count (associated with allergic asthma) would be more likely to receive treatment with omalizumab, while patients with a lower immunoglobulin E count may be more likely to receive mepolizumab to treat the higher eosinophil count. The proportion of the overlap, reported as about 35% by the manufacturer, is not known with certainty.
- The clinical expert noted that among patients who would qualify for both treatments, there is the potential for mepolizumab and omalizumab to be used sequentially upon failure of the other treatment. The model provided to CDR did not consider the possibility of sequential use of mepolizumab and omalizumab, thus the cost-effectiveness of mepolizumab in this setting is unknown.
- The model did not employ a stopping rule. Were a stopping rule implemented, the cost-effectiveness of mepolizumab plus SOC compared with SOC alone may have improved. It is uncertain whether any stopping rule could be operationalized in this setting. The clinical expert consulted by CDR indicated that it may be reasonable to discontinue therapy in the absence of improvement on spirometry after three to four injections.
- One of the observed benefits of mepolizumab observed in trials is its potential OCS-sparing effect. According to the clinical expert consulted by CDR, this is likely to be an important benefit of mepolizumab given the numerous adverse effects associated with frequent or long-term OCS use. The manufacturer attempted to model the benefits of reduced OCS use as part of a scenario analysis; however, neither the total QALYs nor the ICER differed appreciably from the base-case analysis, possibly because of limitations of the data used to model OCS adverse effects. The discordance between the degree of clinical concern surrounding OCS use and its minimal impact in the model represents an important source of uncertainty regarding the results of the analysis, one that could not readily be addressed through CDR reanalysis.
- The patient population in the MENSA trial may not have been representative of the patient population that would receive mepolizumab in Canadian clinical practice. The CDR clinical expert indicated that patients in the MENSA trial may have had more moderate disease based on the observed mean eosinophil counts in this study, while the patient population in the SIRIUS trial may have been more representative of the Canadian patient population.

7. PATIENT INPUT

Input was received from two patient groups: Ontario Lung Association and Asthma Society of Canada/National Asthma Patient Alliance. Information was obtained from these groups through online surveys of asthma patients, input from a certified respiratory educator, a mixed-methods study involving 24 in-depth personal interviews, and an online quantitative survey of 200 individuals.

Patient input indicated that common symptoms and challenges experienced by a person living with asthma included shortness of breath, coughing, wheezing, difficulty fighting infections, and fatigue. The Asthma Society placed particular emphasis on the impact on patients' daily lives, such as decreased physical activity, reduced performance at work or school, restricted social interactions, and increased emergency room visits. Activity restriction as a result of uncontrolled asthma symptoms was of particular concern. Although impact on caregivers was not specifically assessed by the patient groups,

their comments suggested that caregivers may experience an emotional (e.g., stress, anxiety) or financial burden, or both.

According to the patient input, while current therapies provide some relief from symptoms (e.g., shortness of breath, cough, poor appetite, ability to fight infections), there was discontent relating to losses in productivity as a result of medical appointments and associated travel time. In addition, respondents wished for a greater improvement of asthma symptoms with therapy and a reduction in overall medication burden. Particular concern was expressed regarding the use of corticosteroids, as both inhaled corticosteroids and OCS are associated with short-term and long-term adverse effects. Financial constraints and access to medication were also noted as issues.

No patients from the patient-group surveys and studies reported prior use or experience with mepolizumab; however, both patient groups expected mepolizumab would improve quality of life and lung function, leading to optimal asthma control. This would also result in reduced emergency department visits and hospitalizations, decreased sleep disturbances, symptom-free exercise, and improved work performance. The manufacturer's pharmacoeconomic analysis considers quality of life (through QALYs) and exacerbations, but does not consider other potential benefits such as exercise tolerance and work performance.

8. CONCLUSIONS

The results of the pharmacoeconomic analyses undertaken both by CDR and the manufacturer indicated that mepolizumab as an add-on to SOC for adult patients with severe eosinophilic asthma was not cost-effective at conventionally accepted thresholds compared with SOC alone. The CDR base-case analysis, addressing some of the identified limitations, resulted in an ICER of $521,000 per QALY. A price reduction for mepolizumab of 89% is required to obtain an incremental cost-utility ratio of $50,000 per QALY or a price reduction of 80% to obtain an incremental cost-utility ratio of $100,000 per QALY. For jurisdictions that reimburse omalizumab for patients with severe eosinophilic asthma requiring add-on treatment, mepolizumab may be cost-saving compared with omalizumab (at up to [redacted] vials per administration of the latter), but the comparative clinical efficacy and safety of mepolizumab versus omalizumab is uncertain; thus, a conclusion regarding the cost-effectiveness in this comparison cannot be made.

APPENDIX 1: COST COMPARISON

The comparators presented in Tables 3 and 4 have been deemed to be appropriate by clinical experts. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the tables; therefore, the figures in the tables may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR TREATMENTS FOR SEVERE EOSINOPHILIC ASTHMA

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Mepolizumab (Nucala)	100 mg/mL	Vial of powder for SC injection	[redacted]	[redacted]	100 mg every 4 weeks	[redacted]	[redacted]

SC = subcutaneous.
Source: Manufacturer's submitted confidential price.

TABLE 4: COST COMPARISON TABLE FOR OTHER TREATMENTS FOR ASTHMA

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Other Biologics							
Omalizumab (Xolair)	150 mg	Vial (sterile powder for reconstit.)	612.0000[a]	612.00 to 1,836.00	150 to 375 mg is administered SC every 2 or 4 weeks[b]	Low dose: 21.80 High dose: 130.78	Low dose: 7,956 High dose: 47,736
ISC							
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 1,004
Fluticasone propionate (Flovent Diskus)	50 mcg 100 mcg 250 mcg 500 mcg	Inhalant powder (60 doses)	13.9500[c] 23.9300[d] 41.2800 64.2000	0.3988 0.3988 0.6880 1.0700	100 mcg 250 mcg 500 mcg twice daily	0.80 to 2.14	291 to 781

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
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)	35.4800 70.9600	0.5913 1.1827	200/400 mcg once daily	0.59 to 1.18	216 to 432
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 339
Beclomethasone dipropionate (QVAR)	50 mcg 100 mcg	Metered dose aero. inhalation (200 doses)	31.1900 62.2000	0.1560 0.3110	100 to 800 mcg daily, in two doses	0.31 to 2.49	114 to 908
ICS + LABA Combinations							
Budesonide/Formoterol (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	Inhalant powder (120 doses)	64.5600 83.8800	0.5380 0.6990	100/6 mcg or 200/6 mcg twice daily	1.08 to 1.40	393 to 510
Fluticasone propionate/ Salmeterol (Advair)	125/25mcg 250/25mcg	MDI (120 doses)	97.4299 138.3141	0.8119 1.1526	125/25 mcg or 250/25 mcg twice daily	1.62 to 2.30	593 to 841
Fluticasone propionate/ Salmeterol (Advair Diskus)	100/50mcg 250/50mcg 500/50mcg	Inhalant 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	1,185 to 1,683
Fluticasone furoate/ vilanterol trifenatate (Breo Ellipta)	100/25mcg 200/25mcg	Inhalant powder (30 doses)	120.000 NPA	4.0000 NPA	100/25 mcg or 200/25 mcg once daily	4.00 NPA	1,460 NPA
Mometasone furoate/ Formoterol fumarate (Zenhale)	50/5mcg 100/5mcg 200/5mcg	MDI (120 doses)	70.5600 89.5560 108.5400	0.5880 0.7463 0.9045	100/10 mcg 200/10 mcg 400/10 mcg twice daily	2.35 to 3.62	858 to 1,321
LTRAs							
Montelukast (Singulair)	4 mg 5 mg	Chew tab Chew tab	1.5457[d] 1.7120[d]	1.5457 1.7120	Age 6 to 14: 5mg daily Age ≥	1.69 to 2.48	617 to 906

Drug / Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
	10 mg	Tablet	2.5044[d]	2.5044	15: 10 mg daily		
Montelukast (generics)	4 mg 5 mg 10 mg	Chew tab Chew tab Tablet	0.3646[d] 0.5565[d] 0.8195[d]	0.3646 0.5565 0.8195	Age 6 to 14: 5mg daily Age ≥ 15: 10 mg daily	0.56 to 0.82	203 to 299
Zafirlukast (Accolate)	20 mg	Tablet	0.7767[d]	0.7767	20 mg twice daily	1.55	567
LAMA							
Tiotropium (Spiriva Respimat)	2.5 mcg	Solution for inhalation (60 inhal.)	NPA	NPA	2 inhalations (2.5 mcg) once daily	NPA	NPA
OCS							
Prednisone (generic)	1 mg 5 mg 50 mg	Tab	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; IgE = immunoglobulin E; LABA = long-acting beta$_2$ adrenergic agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MDI = metered dose inhaler; NPA = no public price currently available; OCS = oral corticosteroid; SC = subcutaneous; Tab = tablet.

[a] Ontario Drug Benefit Formulary Exceptional Access Program (January 2016).

[b] Dosing is dependent upon body weight and baseline IgE; can range from 150 mg to 300 mg when dosed every 4 weeks, and 225 mg to 375 mg when dosed every 2 weeks.[20]

[c] Quebec Formulary (January 2016).

[d] Saskatchewan Formulary (January 2016).

Source: Ontario Drug Benefit Formulary (accessed January 2016) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

Based on the Manufacturer's Submission to the CADTH Common Drug Review

TABLE 5: BASED ON THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION, WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS MEPOLIZUMAB PLUS SOC RELATIVE TO SOC ALONE?

MEP + SOC vs. SOC Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life		X				
ICER or net benefit calculation	$143,778 per QALY $22,540 per life-year					

ICER = incremental cost-effectiveness ratio; MEP = mepolizumab; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

TABLE 6: BASED ON THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION, WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS MEPOLIZUMAB PLUS SOC RELATIVE TO OMALIZUMAB PLUS SOC?

MEP + SOC vs. SOC Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical Outcomes		X				
Quality of life		X				
ICER or net benefit calculation	MEP + SOC dominated OMA + SOC					

ICER = incremental cost-effectiveness ratio; MEP = mepolizumab; NA = not applicable; OMA = omalizumab; SOC = standard of care; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The model showed inconsistent results due to the source data used. No attempt was made to adjust for the limitations of the source data. The model structure and formulas appear convoluted, and are not entirely transparent.		
Was the material included (content) sufficient?			X
Comments	The model was reported to have been validated, but the validation report was not provided with the initial submission. Much of the information was reported as manufacturer data on file, or analyses undertaken were not part of the CSRs or ITC report.		
Was the submission well organized and was information easy to locate?		X	
Comments	See comments above		

CSR = Clinical Study Report; ITC = indirect treatment comparison.

TABLE 8: AUTHORS' INFORMATION

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

CDR = CADTH Common Drug Review.

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

Mepolizumab for severe eosinophilic asthma is currently under review by the National Institute for Health and Care Excellence in the UK with an anticipated publication date of July 2016.[21] No other health technology assessment organization reviews of mepolizumab for asthma were found.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

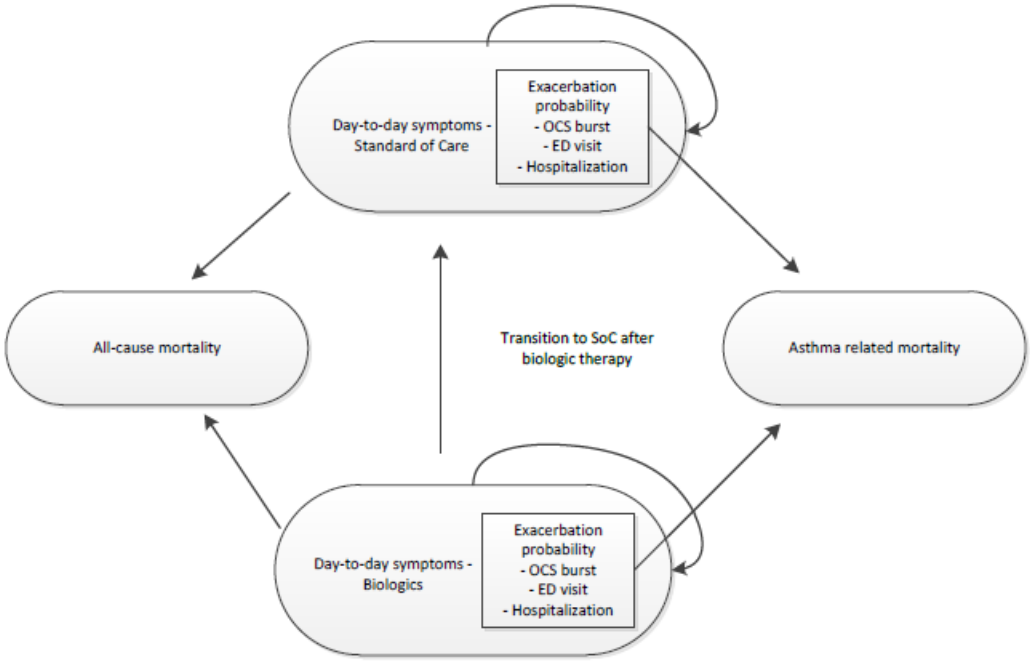
The manufacturer reported that for Canadian provinces that reimburse omalizumab through exceptional access programs, the comparison of mepolizumab plus standard of care (SOC) versus omalizumab plus SOC is relevant for patients with asthma who meet the eligibility criteria for both biologics. In other jurisdictions, the appropriate comparison is mepolizumab plus SOC versus SOC alone.

The manufacturer developed a cohort Markov model in Microsoft Excel 2013 to assess treatment for severe eosinophilic asthma despite best SOC. The model used four health states: day-to-day asthma symptoms for patients receiving a biologic, day-to-day asthma symptoms for patients receiving SOC, asthma-related mortality (ARM) (in hospital and outside hospital), and all-cause mortality. Within the two day-to-day asthma symptoms states, patients could experience three types of exacerbation events: exacerbations requiring a short course of oral corticosteroids (OCSs) for the outpatient treatment of acute severe asthma exacerbations, emergency department visit without being admitted, or hospitalization. The model structure is shown in Figure 1.

Patients begin in one of the "day-to-day symptoms" health states, where they experience symptom-free periods as well as non-clinically significant exacerbations. Patients in these health states have a risk of clinically significant exacerbation, requiring administration of OCS for at least three days, a visit to the emergency department, or hospitalization (as per unpublished data from the MENSA trial),[1] as well as a risk of death in each cycle; these risks differ depending on the treatment. The cycle length used was four weeks based on the recommended dosage regimen for mepolizumab. No half-cycle correction was applied due to the short cycle length. The model time horizon is a patient's lifetime, with a maximum of 10 years of biologic treatment, at which time patients continue on SOC alone and are assigned exacerbation rates and health status based on the SOC group. These patients accrue no residual treatment effects; beyond the initial 10 years of treatment, there are no differences in effects in the biologic treatment group and the SOC group. This time frame was based on a previously published health technology assessment of omalizumab.[22]

When an exacerbation occurs within a cycle, a utility decrement is applied based on the type of exacerbation, and a cost to treat the exacerbation is also applied. The risk of ARM was applied for patients with exacerbations requiring a short course of OCS, emergency department visits, and hospitalizations. The model ran until 99% of patients moved to one of the absorbing states (death from all causes or ARM).

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



ED = emergency department; OCS = oral corticosteroid; SoC = standard of care.
Source: Manufacturer's Pharmacoeconomic Report.[1]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy – type/ rate of exacerbation	MEP + SOC vs. SOC alone: Manufacturer's report indicated that published and unpublished data from MENSA trial were used. Data for MEP 75 mg IV formulation groups were pooled with the 100 mg SC group. Although not stated in the manufacturer's report, the model uses data from the ITC to inform this comparison. MEP + SOC vs. OMA + SOC: Inputs estimated through manufacturer-conducted ITC.	CDR clinical review found substantial limitations with the available ITCs, relating to the inclusion of studies, and heterogeneity in the included studies. Given the uncertainty, CDR was not able to make conclusions about the comparative efficacy and safety of MEP vs. OMA (see CDR Clinical Report). Given that head-to-head data are available from MENSA, it is not appropriate to use data from the ITC for the comparison of MEP + SOC vs. SOC alone. It may not be appropriate to pool data from the IV and SC groups of MENSA given the differing doses and routes of administration.
Natural history — patient characteristics	Patient age, gender, and disease severity based on the MENSA trial.	The CDR clinical expert indicated that the average age may be lower in Canadian clinical practice. According to the clinical expert consulted by CDR, MENSA population may have been less

Data Input	Description of Data Source	Comment
		severe than candidates for MEP therapy in Canadian clinical practice.
Utilities — health states	Health-state utility values were mapped from SGRQ to EQ-5D from the MENSA trial (unpublished data).[1]	The mapping process has not been validated in this patient population (see CDR Clinical Review for more details). The authors who proposed the mapping algorithm concluded "it is in the interests of the manufacturer and HTA body that utility scores be directly derived from the clinical trial population."[23] CDR notes that use of mapped values is generally not preferred and results in increased uncertainty in the values. Actual EQ-5D values were captured in the DREAM trial, but not used in the base-case analysis due to concerns regarding ceiling effects. Feedback from the CDR clinical reviewers indicated the patient population in DREAM was similar to the patient population from MENSA.
Utilities – events	Utility decrements for clinically significant non-severe and severe exacerbations were obtained from Lloyd et al.[24]	The study by Lloyd et al.[24] includes 112 patients, of whom only 27 had exacerbations (22 with no hospitalization, 5 with hospitalization). Thus the sample size calls into question the validity of these values, especially given the substantial variance in the responses. Other literature is available and could have been used to test results.
Adverse events	AE and SAE rates in the MEP and OMA RCTs were generally low and similar between treatment groups, with a small proportion of patients withdrawing due to AE (< 1%). Thus, AEs were not included in the model.	The CDR clinical review indicates there were no notable differences in AE rates between MEP and PBO. ITC did not assess comparative safety of MEP and OMA.
Mortality	ARM sourced from Watson et al.[17] for patients hospitalized, and calculated based on a UK Report[25] for patients who were not hospitalized. Data were calculated by age group. All-cause mortality sourced from Statistics Canada.[26]	Other publications reported for ARM and values tested in SAs.
Resource Use		
Biologics	Derived from use in MENSA trial and PMs, as well as utilization data from IMS Brogan for OMA.	CDR undertook a review of utilization data for OMA, which indicated the potential for fewer vials per administration on average compared with the number of vials assumed in the model.
SOC	Derived from treatments defined as SOC and their use in MENSA trial, and PMs of these treatments.	May be overestimated, but does not significantly affect the results.

Data Input	Description of Data Source	Comment
Administration and monitoring	Based on input from a clinical expert.	
Event (OCS use)	Derived from pooled data from DREAM and MENSA trials. Includes potential resources based on telephone calls, home visit, GP visit, hospital clinic visit, OCS dose.	May be overestimated, but does not significantly affect the results.
Event (ED visit)	Derived from pooled data from the DREAM and MENSA trials. Includes potential resources based on telephone calls, GP visit, hospital clinic visit, OCS dose, ED visit.	May be overestimated, but does not significantly affect the results.
Event (hospitalization)	Derived from pooled data from the DREAM and MENSA trials. Includes potential resources based on telephone calls, home visit, GP visit, hospital clinic visit, OCS dose, ED visit, hospitalization.	May be overestimated, but does not significantly affect the results.
Costs	Costs were measured using 2015 Canadian dollars. Annual CPI from Statistics Canada was used to inflate dated costs.	CPI rates have changed slightly since the report was submitted. CDR updated the CPI rates.
Drug	Manufacturer	
SOC and OCS	Ontario Drug Benefit Formulary and Ontario Drug Benefit Exceptional Access Formulary (June 2015) were used as a proxy for all Canadian jurisdictions.	
Treatment administration and monitoring	Ontario Schedule of Benefits and Fees (June 2015) Payscale.com (nurse wage) (June 2015)	As Ontario is presented as the proxy jurisdiction, the Ontario Nurses Association Collective Bargaining Agreement is also an appropriate source.
Event costs: ED visits and hospitalization	Ontario Case Costing Initiative (2011)	Costs could have been tested from the Alberta Interactive Health Data Application.
Event costs: Telephone calls; home, practice and clinic visits	Payscale.com (nurse wage) (June 2015) Ontario MOHLTC Schedule of Benefits for Physician Services 2015	As Ontario is presented as the proxy jurisdiction, the Ontario Nurses Association Collective Bargaining Agreement is also an appropriate source.

AE = adverse event; ARM = asthma-related mortality; CDR = CADTH Common Drug Review; CPI = Consumer Price Index; ED = emergency department; EQ-5D = EuroQoL 5 Dimensions questionnaire; GP = general practitioner; HTA = health technology assessment; ICS = inhaled corticosteroid; ITC = indirect treatment comparison; IV = intravenous; MEP = mepolizumab; MOHLTC = Ministry of Health and Long-Term Care; OCS = oral corticosteroid; OMA = omalizumab; PBO = placebo; PM = product monograph; RCT = randomized controlled trial; SA = sensitivity analysis; SAE = serious adverse event; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire; SOC = standard of care; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report.[1]

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Utility decrement of exacerbation requiring ED visit is same as for exacerbation requiring short-term OCS.	This appears to be a conservative assumption, as other literature indicates a greater disutility due to exacerbation requiring ED visit. CDR tested revised disutility values.
Duration of utility decrement from exacerbation is assumed to last 4 weeks, corresponding to the follow-up period of 4 weeks.	The manufacturer assumes in the base case that the utility decrement applies to the entire cycle length. This is likely an overestimate in some circumstances: • OCS treatment is likely to last only 7 to 10 days; although an ED visit is likely to last a day, it is likely reasonable to assume that treatment subsequent to the ED visit could affect utility for at least as long as OCS treatment. Therefore, disutility applied over 4 weeks for patients with an ED visit prescribed OCS treatment is likely an overestimate. • For hospitalized patients, the average hospital LOS for asthma is only 3 days. However, feedback from the CDR clinical expert indicated that the assumed duration of impact on quality of life (utility value) of 4 weeks post-hospitalization may be reasonable. Altering duration of the utility decrement for exacerbations does not have a large impact on the ICER.
QoL data for asthma symptom health states for MEP were applied to OMA.	This is appropriate.
The OCS burst regimen is best informed by NAEPP guidelines (40 mg to 60 mg for 5 days to 10 days); which resulted in an assumption of the expected total dose of prednisone as 350 mg.	This may be an overestimate; feedback from the CDR clinical expert indicated that OCS is more likely to be dosed at 25 mg to 40 mg for 7 days to 10 days, thus a lower dose may be more appropriate. Due to the low cost of OCS, this does not have a large impact on the model results.
Exacerbations are classified into 3 categories defined by the resources incurred.	This is generally accepted as appropriate, although the severity of the exacerbation resulting in hospitalization may also affect utility values, costs, and resource use.
Duration of biologic treatment assumed to be 10 years.	While this appears to be consistent with other published economic evaluations (e.g., Norman et al.),[22] there is little long-term experience with MEP. The CDR clinical expert indicated that in the absence of other options, and if the patient continues to respond, it is reasonable to expect the patient to continue biologic treatment over the long term. Due to uncertainty in the long-term benefits and harms of MEP, this parameter was tested by CDR.
No residual treatment effect when patients stop biologic treatment after 10 years.	This may be a conservative assumption.
All patients in the MEP + SOC group received MEP for up to 10 years; no patients discontinued treatment with MEP in that time period, regardless of effect.	It is unlikely that MEP will be effective in all patients; 37 patients withdrew in the MENSA trial (25 MEP, 12 PBO). If a stopping rule was created for patients who were not responding to treatment after a certain time point, this may improve the cost-effectiveness of MEP.

Assumption	Comment
Exclusion of long-term OCS and related impacts in the base case.	This may be appropriate, given the lack of long-term data on OCS safety and efficacy in the population of interest. Manufacturer performed scenario analysis to model OCS effects.
ARM occurs because of severe exacerbations (those requiring short-term OCS, ED visit, hospitalization).	Reasonable assumption.
All-cause mortality was not adjusted for ARM.	May be reasonable as ARM represents a very small fraction of overall mortality, although given the lifetime time horizon, this may inappropriately reduce the number of patients toward the end of the model time horizon.

ARM = asthma-related mortality; CDR = CADTH Common Drug Review; ED = emergency department; ICER = incremental cost-effectiveness ratio; LOS = length of stay; MEP = mepolizumab; NAEPP = National Asthma Education and Prevention Program; OCS = oral corticosteroid; OMA = omalizumab; PBO = placebo; QoL = quality of life; SOC = standard of care.

Validation

The manufacturer undertook a technical validation of the model that considered potential transcription error, lack of internal or external validity, and any omissions or bias; it was performed by an analyst not involved in the model adaptation. Findings were indicated to have been documented in a written validation report and addressed. The validation report was not provided by the manufacturer.

Manufacturer's Sensitivity Analysis

The manufacturer undertook both deterministic and probabilistic sensitivity analyses to determine the influence of uncertainty surrounding input parameters. Parameter estimates were varied within the uncertainty distributions that best reflected the nature of each parameter where values were available, or a standard error of 20% was assumed around the mean value.

Inputs tested in the deterministic sensitivity analysis include exacerbation rate for biologics and SOC, results of the indirect treatment comparison (ITC), clinical efficacy for omalizumab, ARM by age group, utility values (based on EuroQoL 5-Dimensions questionnaire [EQ-5D] values and St. George's Respiratory Questionnaire [SGRQ] mapped to EQ-5D), utility decrements due to exacerbations, duration of treatment administration and costs, resource use for exacerbations, and cost of exacerbations.

The multivariate probabilistic sensitivity analysis used 2,000 simulations to test the uncertainty of model results. The results of these analyses were presented via scatter plot and a cost-effectiveness acceptability curve to estimate the probability of mepolizumab being considered cost-effective against the comparators at a given willingness-to-pay threshold per quality-adjusted life-year (QALY) gained. The multivariate probabilistic sensitivity analysis tested the same parameters as the deterministic sensitivity analysis, as well as using an alternate source to estimate the proportion of patients with exacerbation experiencing each exacerbation subtype.

Manufacturer's Scenario Analysis

The manufacturer undertook several scenario analyses to explore the sensitivity of the economic results to key structural and data assumptions used in the model. The scenarios tested are presented in Table 11.

TABLE 11: MANUFACTURER'S SCENARIO ANALYSES

Parameter	Base-Case Analysis	Alternative Scenario Tested
Patient age	50.1 years	30 years, 65 years
Treatment duration	10 years	1 year, 5 years, lifetime[a]
Time horizon	Lifetime	1 year, 5 years, 10 years, 20 years
Asthma-related mortality	Watson et al. 2007[17]	Roberts et al. 2013
Health-state utilities	SGRQ mapped to EQ-5D	EQ-5D
Duration of utility decrement	Lloyd et al. 2007[24]	MENSA trial (unpublished)[1]
Indirect evidence for biologics	Licensed indication	Overlap indication
Clinical efficacy of omalizumab	ITC/INNOVATE	EXALT trial
Inclusion of long-term OCS	No	Yes, 24% of patients on OCS
Discount rate	5%	0%, 10%

OCS = oral corticosteroid; ITC = indirect treatment comparison; INNOVATE = Investigation of Omalizumab in Severe Asthma Treatment; EQ-5D = EuroQoL 5-Dimensions questionnaire; SGRQ = St. George's Respiratory Questionnaire.
[a] Treatment duration cannot be longer than the time horizon selected.
Source: Manufacturer's Pharmacoeconomic Report.[1]

Manufacturer's Results

The manufacturer's analysis indicated that over a lifetime time horizon (patients on biologics for 10 years), patients who received mepolizumab plus SOC had fewer total exacerbations, more life-years, and QALY gains compared with omalizumab plus SOC and SOC alone. Patients receiving omalizumab plus SOC accrued the highest total costs, followed by patients receiving mepolizumab plus SOC, and then patients receiving SOC alone. The cost-effectiveness results are presented in Table 12.

TABLE 12: MANUFACTURER'S BASE-CASE RESULTS

Parameter	MEP + SOC	OMA + SOC	SOC	MEP + SOC vs. OMA + SOC	MEP + SOC vs. SOC
Biologic costs	$[redacted]	$[redacted]	NA		
SOC costs	$[redacted]	$[redacted]	$[redacted]		
Other costs	$[redacted]	$[redacted]	$[redacted]		
Total Costs	**$167,100**	**$232,293**	**$42,258**	**–$65,192**	**$124,842**
Life-years	14.59	14.32	14.08		
QALYs	11.09	10.86	10.22	0.226	0.868
Exacerbations	15.02	17.72	20.56	2.700	5.539
Incremental Cost Per QALY				**Dominant**	**$143,778**
Incremental Cost Per Exacerbation Avoided				**Dominant**	**$22,540**

MEP = mepolizumab; OMA = omalizumab; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report.[1]

Manufacturer's Sensitivity Analysis

The manufacturer's deterministic sensitivity analyses indicated the model was most sensitive to changes in the relative risk of exacerbations and the source for the utility inputs. When the values for these parameters were altered, the incremental cost-effectiveness ratio (ICER) for mepolizumab plus SOC versus SOC alone ranged from $115,000 per QALY to $189,000 per QALY. In all the parameters tested in the deterministic sensitivity analysis for mepolizumab plus SOC versus omalizumab plus SOC,

mepolizumab plus SOC remained dominant (i.e., less costly with greater QALYs; the ICER ranged from −$195,741 to –$747,800 per QALY).

The manufacturer reported that the multivariate probabilistic sensitivity analysis with 2,000 simulations generated an ICER of $143,162 for mepolizumab plus SOC versus SOC alone. Mepolizumab plus SOC dominated omalizumab plus SOC, with higher QALYs and lower costs. The cost-effectiveness acceptability curve indicated that at a willingness-to-pay of $50,000, the probability of mepolizumab plus SOC being cost-effective compared with SOC alone was 0%. At a willingness-to-pay of $100,000, the probability that mepolizumab plus SOC is cost-effective was < 1%. The CADTH Common Drug Review (CDR) notes that the probabilistic sensitivity analysis in the model output reported a slightly higher ICER ($144,028) than was reported in the manufacturer's report.

Manufacturer's Scenario Analysis

The manufacturer undertook several scenario analyses. The results of the scenario analyses are provided in Table 13.

TABLE 13: RESULTS OF MANUFACTURER'S SCENARIO ANALYSES

Parameter	Base-Case Input/Source	Scenario Value	Incremental Cost	Incremental QALYs	ICER (DSA)
Base case			$124,842	0.868	$143,778
Patient age	50.1	30 65	$127,281 $119,056	0.587 0.741	$216,839 $160,724
Treatment duration	10 years	1 year 5 years Lifetime	$16,922 $71,777 $242,642	0.126 0.508 1.588	$134,358 $141,301 $152,770
Time horizon	Lifetime	1 year[a] 5 years[b] 10 years 20 years	$16,806 $71,099 $123,872 $124,443	0.069 0.322 0.618 0.767	$244,917 $221,037 $200,410 $162,260
Asthma-related mortality	Watson et al. 2007	Roberts et al. 2013	$125,753	0.630	$199,520
Non-hospital asthma mortality		+20% –20%	$124,667 $125,012	0.911 0.824	$136,887 $151,664
Health-state utility value	SGRQ mapped to EQ-5D	EQ-5D	$124,842	0.513	$243,291
Duration of utility decrement	Lloyd et al. 2007	MENSA trial	$124,842	0.845	$147,765
Exacerbation rate for MEP vs. OMA	MEP licensed indication	Overlap in population	$124,824	0.864	$144,460
Include long-term OCS impact	No	Yes: Median OCS dose reduction Yes: Proportion w/ total OCS discontinuation	$124,825 $124,841	0.869 0.868	$143,673 $143,761
Discount rate	5%	0% 10%	$158,695 $101,719	1.504 0.603	$105,489 $168,684

Parameter	Base-Case Input/Source	Scenario Value	Incremental Cost	Incremental QALYs	ICER (DSA)
Prescription fee for MEP per 28 days	$0	$8.83	$125,727	0.868	$144,796

DSA = deterministic sensitivity analysis; EQ-5D = EuroQoL 5-Dimensions questionnaire; ICER = incremental cost-effectiveness ratio; MEP = mepolizumab; OCS = oral corticosteroid; OMA = omalizumab; QALY = quality-adjusted life-year; SGRQ = St. George's Respiratory Questionnaire; vs. = versus.
[a] Both treatment duration and time horizon had to be set to 1 year to run this analysis.
[b] Both treatment duration and time horizon had to be set to 5 years to run this analysis.
Source: Manufacturer's Pharmacoeconomic Report.[1]

CADTH Common Drug Review Reanalyses

CDR identified several limitations with the manufacturer's analyses. CDR undertook a series of scenario analyses to test the impact of revised parameter estimates.

Uncertainty and Inconsistency Associated With Age at Model Entry

The model is sensitive to the patient age at entry. In the manufacturer's base case, the age of entry is 50.1 years (ICER is $143,778 per QALY). The CDR clinical expert indicated that patients in Canadian clinical practice are younger than the average age used in the model. CDR tested a range of ages at entry, but noted that the results were inconsistent. Due to the model structure and assumptions, the use of an average age in this circumstance is not likely to be representative of the cost-effectiveness in the patient population as ages at both the higher and lower bounds resulted in higher ICERs for mepolizumab plus SOC compared with SOC alone than ICERs derived using the average age. CDR notes that the "lifetime" time horizon model ran for 60 years after the patient's age at entry – meaning that when age at entry was 30, the model ran until age 90; and when age at entry was 50, the model ran until age 110 (although it appears no patients were in the model past age 106). The inconsistency associated with ICERs based on age at model entry appears to be due to the use of rates stratified by age group. The source data provided ARM rates for ages 17 to 44 (0.38%) and 45 and older (2.48%). The results of the CDR scenario analysis are reported in Table 14.

Time Horizon

The manufacturer's use of a lifetime time horizon is appropriate in principle, but given the issues identified with the modelling of age at model entry, there is substantial uncertainty regarding the modelling of mepolizumab over a longer term. As noted in the preceding section, above, the "lifetime" time horizon was actually 60 years from the age at entry to the model. If the age at model entry was 30, clinical benefits, QALYs, and costs were accrued until age 90. However, in testing the time horizon, CDR notes that the uncertainty in the model seems to appear after patients' transition from receiving mepolizumab plus SOC to SOC alone after the 10-year duration of biologic therapy. The proportion of patients who experience exacerbations after 10 years is higher for patients who initially received mepolizumab than for patients who received only SOC; this continues for the rest of the model, which results in inconsistencies over the longer time horizon. There are limited long-term data available regarding patient outcomes, particularly after discontinuation of biologic treatment. CDR notes that the majority of the benefits associated with quality of life are accrued in the initial 10 years in the model. Beyond 10 years, the incremental benefits accrued are associated with an assumption of life extension. Thus, to attempt to reduce uncertainty in the results, CDR restricted the time horizon to 10 years (as per the assumed duration of biologic treatment). The use of a 10-year time horizon increased the ICER

(Table 14). CDR also undertook a multi-way analysis to determine the extent to which age at entry impacted the model with a 10-year time horizon (Table 15).

Uncertainty Associated With Duration of Treatment With Biologic Treatment

The manufacturer's base case assumed that the duration of biologic treatment was 10 years. The CDR clinical expert noted that there is little information available to determine how long biologics will be used in this patient population, especially relating to mepolizumab. Although there is no information regarding the effects of mepolizumab use over a longer time period (i.e., treatment waning, safety concerns), the CDR clinical expert indicated that if a patient responds to treatment and maintains response, treatment is likely to be continued long term. CDR notes that the ICER slightly increases as the duration of biologic treatment increases. The manufacturer tested other durations of biologic treatment, including one year, five years, and lifetime (Table 13). However, as there is no reliable estimate or assumption around duration of biologic treatment, and a duration of 10 years has been used in other health technology assessments[22] for similar patient populations (severe persistent allergic asthma), CDR did not revise the base-case treatment duration in the multi-way analysis.

Use of Mapped Health-State Utility Values When Direct Values Were Available

The model is sensitive to the health-state utility values used. As per one of the manufacturer's scenario analyses, when using the EQ-5D values collected directly by the manufacturer in the DREAM trial, the ICER for mepolizumab plus SOC compared with SOC alone increases from $143,778 to $243,291 per QALY. The results of probabilistic sensitivity analyses based on these utility inputs are similar to the deterministic analysis results.

CDR notes that the manufacturer chose values that were mapped from an asthma and chronic obstructive pulmonary disease–specific quality-of-life questionnaire (SGRQ); the mapping algorithm does not appear to have been validated in the severe eosinophilic asthma patient population in the literature (see CDR Clinical Review for more details). The authors who proposed the mapping algorithm concluded that "it is in the interests of the manufacturer and [health technology assessment] body that utility scores be directly derived from the clinical trial population."[23] CDR determined that, given the limited validity of the mapping procedure used and the availability of direct utility values, the directly derived utility values were most appropriate for the CDR analyses (Table 14).

Inconsistency in Utility Value Sources for Health States and Events

Although the manufacturer used health-state utility values based on mapped values, it used a source that used directly derived values for the disutilities due to exacerbation. Given the manufacturer's argument that mapped values are appropriate, it is uncertain why the manufacturer chose to use a source that used directly derived values given the availability of other values based on mapping procedures.[18,19] CDR undertook scenario analyses using other published utility values for both the health state and event disutilities (exacerbations) from Campbell et al.[19] and Zafari et al.[18] CDR notes that although both of these studies are based on values mapped from the Asthma Quality of Life Questionnaire to the EQ-5D, these revised analyses were undertaken to highlight the uncertainty associated with the utility values used and the impact of this uncertainty on the ICER. The scenario analyses based on the Campbell et al. and Zafari et al. studies resulted in ICERs ranging from $137,000 to $178,000 per QALY for mepolizumab plus SOC compared with SOC alone (Table 14). Mepolizumab plus SOC continued to dominate omalizumab plus SOC when these utility values were used.

Uncertainty Surrounding the Results of the Indirect Treatment Comparison

CDR identified two ITCs comparing mepolizumab with omalizumab but focused on the ITC submitted by the manufacturer. The manufacturer's ITC for the comparison of mepolizumab plus SOC to omalizumab plus SOC was based [redacted]. CDR reviewers observed that the findings of the ITC should be interpreted with extreme caution due to the heterogeneity of the included studies. CDR clinical reviewers found that due to serious limitations with the analysis and a high degree of uncertainty associated with the findings, no conclusion can be drawn regarding the comparative effectiveness and safety of mepolizumab with omalizumab in the treatment of severe asthma. Given the uncertainty of the clinical findings, CDR undertook an analysis assuming no comparative efficacy benefit for mepolizumab over omalizumab; i.e., a cost-minimization analysis assuming no difference in QALY gains. When equivalent efficacy was assumed and all other assumptions were unchanged, mepolizumab was found to be cost-saving compared with omalizumab (Table 14). CDR did not undertake analyses assuming mepolizumab was less effective than omalizumab.

Choice of Clinical Evidence for Mepolizumab Plus SOC Compared With SOC Alone

The manufacturer's base case uses data from the ITC for the mepolizumab plus SOC treatment group while using data from the head-to-head study for the treatment group receiving SOC alone. Given that there is direct evidence available from the MENSA trial, and in light of the heterogeneity in the ITC, the use of data from the ITC for this comparison is not ideal. When direct evidence from the MENSA trial was used for the comparison of mepolizumab plus SOC to SOC alone, the ICER increased to $146,305 per QALY (Table 14).

Dose of Omalizumab

The manufacturer assumed 3.15 vials of omalizumab per administration based on utilization data from IMS Brogan, which was not provided.[14] CDR undertook a review of utilization data and found the average number of units per claim to be approximately 2.35 vials. The CDR clinical expert indicated that the average dose is likely to be approximately 300 mg per four-week period (two vials). CDR undertook a reanalysis testing the impact of these alternative values (Table 14).

CDR notes that the dose used in the trial of omalizumab that the manufacturer used in its ITC could not be compared with utilization from claims data, as this dose is not reported in the public domain. As the dose of omalizumab is based on weight (and immunoglobulin E levels), the patient's weight affects the number of vials used and, thus, the cost relative to mepolizumab.

TABLE 14: RESULTS OF CADTH COMMON DRUG REVIEW ONE-WAY ANALYSES

Parameter Being Tested	MEP + SOC vs. OMA + SOC			MEP + SOC vs. SOC Alone		
	Cost	QALYs	ICER	Cost	QALYs	ICER
Patient Age at Model Entry						
30 years	–$69,752	0.066	Dominant	$127,281	0.587	$216,839
35 years	–$69,676	0.064	Dominant	$127,117	0.582	$218,285
40 years	–$68,519	0.141	Dominant	$126,975	0.724	$175,282
45 years	–$65,486	0.239	Dominant	$125,602	0.896	$140,175

Parameter Being Tested	MEP + SOC vs. OMA + SOC			MEP + SOC vs. SOC Alone		
	Cost	QALYs	ICER	Cost	QALYs	ICER
50.1 years (base case)	–$65,192	0.226	Dominant	$124,842	0.868	$143,778
55 years	–$64,721	0.210	Dominant	$123,711	0.835	$148,179
60 years	–$63,919	0.191	Dominant	$121,903	0.793	$153,796
65 years	–$62,594	0.169	Dominant	$119,056	0.741	$160,724
70 years	–$60,431	0.144	Dominant	$114,581	0.678	$169,061
Time Horizon						
Lifetime (base case)	–$65,192	0.226	Dominant	$124,842	0.868	$143,778
10 years	–$65,722	0.096	Dominant	$123,872	0.618	$200,410
Utility Values						
EQ-5D mapped from SGRQ (base case)	–$65,192	0.226	Dominant	$124,842	0.868	$143,778
EQ-5D from DREAM trial	–$65,192	0.237	Dominant	$124,842	0.513	$243,291
Campbell et al. 2010	–$65,192	0.225	Dominant	$124,842	0.906	$137,807
Zafari et al. 2016	–$65,192	0.211	Dominant	$124,842	0.704	$177,304
Comparative Evidence: MEP + SOC vs. SOC						
ITC (base case)	NA	NA	NA	$124,842	0.868	$143,778
MENSA trial	NA	NA	NA	$124,776	0.853	$146,305
Comparative Evidence: MEP + SOC vs. OMA + SOC						
ITC (base case)	–$65,192	0.226	Dominant	NA	NA	NA
No difference in efficacy	[redacted]	0.000	MEP is cost-saving	NA	NA	NA
Vials of OMA Per Cycle						
2 vials	[redacted]	0.226	[redacted]	NA	NA	NA
2.35 vials	[redacted]	0.226	Dominant	NA	NA	NA
3.15 vials (base case)	–$65,192	0.226	Dominant	NA	NA	NA

CDR = CADTH Common Drug Review; EQ-5D = EuroQoL 5 Dimensions; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MEP = mepolizumab; NA = not applicable; OMA = omalizumab; QALY = quality-adjusted life-year; SGRQ = St George Respiratory Questionnaire; SOC = standard of care; vs. = versus.

TABLE 15: RESULTS OF CADTH COMMON DRUG REVIEW MULTI-WAY ANALYSIS

Parameter Being Tested	MEP + SOC vs. OMA + SOC			MEP + SOC vs. SOC Alone		
	Cost	QALYs	ICER	Cost	QALYs	ICER
Patient Age at Model Entry, Based on 10-Year Time Horizon						
30 years	–$69,859	0.037	Dominant	$127,126	0.529	$240,376
40 years	–$68,883	0.051	Dominant	$126,325	0.549	$230,059
50 years	–$65,733	0.096	Dominant	$123,893	0.618	$200,406
60 years	–$64,319	0.093	Dominant	$121,172	0.603	$200,817
70 years	–$60,666	0.086	Dominant	$114,150	0.565	$201,948

ICER = incremental cost-effectiveness ratio; MEP = mepolizumab; OMA = omalizumab; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

CADTH Common Drug Review Base-Case Analysis

CDR undertook a multi-way analysis assessing the limitations identified earlier that could be addressed in the model (i.e., revised assumptions for utility values, model time horizon, choice of clinical evidence

for comparison with SOC alone, comparative effectiveness of omalizumab and mepolizumab for comparison with omalizumab plus SOC, and dose of omalizumab):

- Time horizon was set to 10 years to reduce uncertainty in the results related to anomalous results for different ages at model entry.

- Direct utility values for the day-to-day symptom health states from the DREAM trial were used.
- For the comparison of mepolizumab plus SOC to SOC alone, data from the head-to-head study (MENSA) were used due to the heterogeneity observed in the ITC.
- Due to the aforementioned limitations of the ITC, the CDR base-case analysis for mepolizumab plus SOC versus omalizumab plus SOC assumed no difference in clinical efficacy (i.e., QALY difference of 0).
- For the comparison of mepolizumab plus SOC to omalizumab plus SOC, the average number of vials used for omalizumab was assumed to be 2.35 based on CDR's review of the available Pharmastat claims data.

The results of the CDR base-case analysis are presented in Table 16.

TABLE 16: RESULTS OF CADTH COMMON DRUG REVIEW BASE-CASE ANALYSIS

	MEP + SOC vs. OMA + SOC			MEP + SOC vs. SOC Alone		
	Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
Manufacturer's base case	–$65,192	0.226	Dominant	$124,842	0.868	$143,778
CADTH Common Drug Review base case	[redacted]	0.000	MEP is cost-saving	$123,841	0.237	$521,838

ICUR = incremental cost-utility ratio; MEP = mepolizumab; OMA = omalizumab; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Nucala, lyophilized powder for subcutaneous injection, 100mg/mL. Company: GlaxoSmithKline Inc.. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): GlaxoSmithKline Inc.; 2015 Dec 18.
2. Omalizumab [Internet]. Ottawa: CADTH; 2005 Oct 13. [cited 2016 Mar 15]. Available from: https://www.cadth.ca/omalizumab-15
3. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012 Aug 18;380(9842):651-9.
4. Clinical Study Report: MEA115588. A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma [**CONFIDENTIAL** internal manufacturer's report]. Brentford (UK): GlaxoSmithKline; 2015 Mar 31.
5. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep 25;371(13):1198-207.
6. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014 Sep 25;371(13):1189-97.
7. Clinical Study Report: MEA115575. A randomized, double-blind, placebo-controlled, parallel-group, multicenter study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma [**CONFIDENTIAL** internal manufacturer's report]. Brentford (UK): GlaxoSmithKline; 2014 May 22.
8. Zhang S, Stynes G, Cockle S, et al. Indirect treatment comparison (ITC) of mepolizumab versus omalizumab in the treatment of adults and adolescents (aged 12 years or older) with severe asthma [**CONFIDENTIAL** internal report]. Mississauga (ON): GlaxoSmithKline Inc. Canada;
9. Nucala (mepolizumab): lyophilized powder for subcutaneous injection [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2015 Dec 3.
10. Health Data Branch Web Portal. Toronto: Ministry of Health and Long Term Care. OCCI costing analysis tool; 2015
11. Schedule of benefits for physician services under the Health Insurance Act [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2016 Mar 1. [cited 2016 Mar 15]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
12. Registered nurse (RN) in Toronto, Ontario salary (Canada) [Internet]. Seattle (WA): PayScale Inc.; 2016. [cited 2016 Mar 15]. Available from: http://www.payscale.com/research/CA/Job=Registered_Nurse_(RN)/Hourly_Rate/6d1adc3a/Toronto-ON
13. Table 326-0021. Consumer price index: annual (2002=100) [Internet]. Ottawa: Statistics Canada; 2015. [cited 2016 Mar 15]. Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=3260021&paSer=&pattern=&stByVal=1&p1=1&p2=37&tabMode=dataTable&csid
14. Tracking the utilization of Xolair patients in Canada - results meeting, v.1.0 2014 Oct. Kanata (ON): IMS Health Canada Inc.; 2014.

15. Exceptional Access Program. Drug benefit prices (DBPs) for products reimbursed under the EAP [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2015. [cited 2016 Mar 15]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx

16. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2015 [cited 2016 Mar 15]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/

17. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med [Internet]. 2007 Aug [cited 2016 Jan 29];101(8):1659-64. Available from: http://www.sciencedirect.com/science/article/pii/S0954611107001266

18. Zafari Z, Sadatsafavi M, Marra CA, Chen W, FitzGerald JM. Cost-Effectiveness of Bronchial Thermoplasty, Omalizumab, and Standard Therapy for Moderate-to-Severe Allergic Asthma. PLoS ONE [Internet]. 2016 [cited 2016 Mar 14];11(1):e0146003. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4709059

19. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. Allergy. 2010 Sep;65(9):1141-8.

20. PrXolair® (omalizumab): sterile powder for reconstitution 150 mg vial [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2016 Jan 6.

21. NICE guidance [Internet]. London: National Institute for Health and Care Excellence. Asthma (eosinophilic, severe) - mepolizumab [ID798]; 2016 [cited 2016 Mar 15]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag519 Anticipated publication date: July 2016.

22. Norman G, Faria R, Paton F, Llewellyn A, Fox D, Palmer S, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess. 2013 Nov;17(52):1-342.

23. Starkie HJ, Briggs AH, Chambers MG, Jones P. Predicting EQ-5D values using the SGRQ. Value Health. 2011 Mar;14(2):354-60.

24. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. Prim Care Respir J. 2007 Feb;16(1):22-7.

25. Why asthma still kills [Internet]. London: Royal College of Physicians (UK); 2015. 115 p. [cited 2016 Mar 15]. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills

26. Table 1. Complete life table, Canada 2009 to 2011 [Internet]. Ottawa: Statistics Canada; 2013 Sep 25. [cited 2016 Mar 14]. Available from: http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm