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CADTH COMMON DRUG REVIEW

Request for Advice

MEPOLIZUMAB (NUCALA)

(GlaxoSmithKline Inc.)

Indication: Severe eosinophilic asthma.

Service Line:	CADTH Common Drug Review
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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

ACQ	Asthma Control Questionnaire
ACQ-5	Asthma Control Questionnaire 5
ACQ-6	Asthma Control Questionnaire 6
ACQ-7	Asthma Control Questionnaire 7
AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
FEV_1	forced expiratory volume in one second
FP	fluticasone propionate
ICC	intraclass correlation coefficient
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
IL-5	interleukin-5
INESSS	Institut national d'excellence en santé et services sociaux
ITC	indirect treatment comparison
LABA	long-acting beta2 agonist
MCID	minimal clinically important difference
OCS	oral corticosteroid
OLA	Ontario Lung Association
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SABA	short-acting beta agonist
SC	subcutaneous
SOC	standard of care

Drug	Mepolizumab (Nucala)
Indication	As 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., long-acting beta2 agonist), and • have a blood eosinophil count of ≥ 150 cells/µL (0.15 GI/L) at initiation of treatment with mepolizumab OR ≥ 300 cells/µL (0.3 GI/L) in the past 12 months.
Original reimbursement request from the manufacturer	For the treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/µL at treatment initiation or ≥ 300 cells/µL 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)	100 mg/mL lyophilized powder for subcutaneous injection
NOC date	December 3, 2015
Manufacturer	GlaxoSmithKline Inc.

Background

The 2016 CADTH Canadian Drug Expert Committee (CDEC) Recommendation, Reasons for the Recommendation, and Of Note sections for mepolizumab as an add-on maintenance treatment of adult patients with severe eosinophilic asthma state the following:

CDEC Recommendation for Mepolizumab (Nucala)

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mepolizumab be reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids (ICS) and one or more additional asthma controller(s) (e.g., a long-acting beta-agonist [LABA]), and have a blood eosinophil count of ≥ 150 cells/mcL at initiation of treatment with mepolizumab or ≥ 300 cells/mcL in the past 12 months, if one of the following clinical criteria and both conditions are met:

Clinical Criteria:

1. Patients who have experienced two or more clinically significant asthma exacerbations in the past 12 months and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry)
2. Are treated with daily oral corticosteroids (OCS).

Conditions

1. Patients should be managed by a physician with expertise in treating asthma.
2. Substantial reduction in price.

Reasons for Recommendation

1. Evidence from two phase 3, double-blind, randomized placebo-controlled trials supports the safety and efficacy of mepolizumab. In MENSA (N = 576), mepolizumab was associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo at 32 weeks in patients currently on high-dose ICS and one or more additional asthma controller(s). In SIRIUS, (N = 135) mepolizumab was associated with a greater likelihood of a reduction in daily OCS dose at 24 weeks compared with placebo in patients currently on high-dose ICS and one or more additional asthma controller(s), and who were taking OCS at a dose of 5 mg/day to 35 mg/day.

Reasons for Recommendation

2. At the submitted price of [redacted] per vial, the CADTH Common Drug Review (CDR) estimated that mepolizumab plus standard of care (SOC) is associated with an incremental cost-effectiveness ratio (ICER) of $521,000 per quality-adjusted life-year (QALY) compared with SOC alone in the treatment of adults with severe eosinophilic asthma; therefore, mepolizumab is not considered to be cost-effective at the submitted price.

Of Note

1. For the comparison of mepolizumab plus SOC with SOC alone, CDEC noted that a price reduction for mepolizumab of 89% is required to achieve an ICER of $50,000 per QALY, or 80% to achieve an ICER of $100,000 per QALY.
2. The manufacturer submitted an indirect treatment comparison (ITC) to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe eosinophilic asthma who would be eligible for both therapies. The CADTH CDEC identified some serious limitations in this ITC and noted a high degree of uncertainty associated with its findings. Therefore, no firm conclusion could be drawn regarding the comparative effectiveness, safety, and cost-effectiveness of mepolizumab versus omalizumab in the treatment of severe eosinophilic asthma.

The primary conclusions for the 2016 CADTH Common Drug Review (CDR) clinical review were as follows:

Two international, manufacturer-sponsored, phase III, double-blind, placebo-controlled randomized controlled trials (RCTs) met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab subcutaneous (SC) 100 mg and mepolizumab IV 75 mg once every four weeks as adjunctive therapy in patients with severe eosinophilic asthma. SIRIUS (N = 135) was a 24-week corticosteroid sparing study that evaluated the effect of mepolizumab SC 100 mg once every four weeks in reducing oral corticosteroid (OCS) use in patients with severe eosinophilic asthma. Results from MENSA suggested that mepolizumab 100 mg SC is associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo in patients currently on high-dose inhaled corticosteroids (ICSs) and an additional asthma controller meeting screening eosinophil criteria of ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the past year. Results from SIRIUS suggested that mepolizumab 100 mg SC is associated with a greater likelihood of a reduction in daily OCS dose compared with placebo in patients with severe eosinophilic asthma who were taking OCS at a dose of 5 mg to 35 mg per day. Due to the increased number of exacerbations in the placebo groups compared with the mepolizumab groups, there was greater unplanned health resource use and use of OCS in the placebo groups. Adverse event (AE) data were generally similar between groups, except for a higher proportion of patients in the placebo groups experiencing asthma-related AEs than in the mepolizumab groups. Safety results from Study MEA115666, a 52-week open-label extension study of patients completing MENSA and SIRIUS, were similar to the AE profile observed in the individual studies.

There were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review. The manufacturer submitted an indirect treatment comparison (ITC) to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies. The results of the ITC suggested that mepolizumab was similar in efficacy to omalizumab with regards to reducing clinically significant exacerbations, hospitalization, improving forced expiratory volume in one second (FEV_1), and AEs. However, there were serious limitations with the analyses due to the limited number of studies included and a high degree of uncertainty associated with the findings.

Request for Advice

CDEC has recommended that mepolizumab, reslizumab, and benralizumab be reimbursed with clinical criteria and conditions for the treatment of eosinophilic asthma. However, there are differences across the three CDEC recommendations with respect to the clinical criteria and conditions. These differences may result in implementation challenges for the jurisdictions.

The CDR participating drug plans are requesting that CDEC provide advice regarding the following:

1. Should the clinical criteria in the CDEC recommendations for mepolizumab and/or reslizumab be updated to align with those that were specified in the more recent CDEC recommendation for benralizumab?
2. If the clinical criteria in the benralizumab recommendation should not be applied to the recommendations for mepolizumab and reslizumab, would it be appropriate for CDEC to establish new clinical criteria that are aligned for all three products?
3. If aligned criteria would not be appropriate for benralizumab, mepolizumab, and reslizumab, could CDEC provide the rationale why different criteria are required for these drugs? Specifically, for mepolizumab and reslizumab, is it appropriate to have to demonstrate reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry) as a clinical criterion for eligibility?

CADTH Common Drug Review Approach to the Request for Advice

To address the questions in the Request for Advice, CADTH conducted a detailed comparison of the included studies in each of the CDR reviews for mepolizumab, reslizumab, and benralizumab with respect to eligibility criteria and the baseline characteristics of the patients included in those studies, as well as a comparison of the Place in Therapy sections that are based on information provided in draft form by the clinical expert(s) consulted by CDR reviewers.

Clinical Findings

CDEC considered the following information during its original deliberations on mepolizumab:

- a systematic review of two double-blind RCTs of mepolizumab
- a critique of the manufacturer's pharmacoeconomic evaluation
- input from a clinical expert with experience in treating patients with severe eosinophilic asthma
- patient group–submitted information about outcomes and issues important to patients
- the manufacturer-submitted ITC.

Patient Input Information

Two patient groups, the Ontario Lung Association (OLA) and the Asthma Society of Canada / National Asthma Patient Alliance, responded to the CDR call for patient input. OLA obtained information from a small number of online surveys, while the Asthma Society of Canada / National Asthma Patient Alliance obtained information from personal interviews and an online quantitative survey. The following is a summary of information provided by the patient groups:

- Asthma symptoms, including shortness of breath, coughing, wheezing, difficulty fighting infections, and fatigue, negatively impact the day-to-day lives of patients. Specifically, patients reported decreased physical activity, reduced performance at work or school, and social isolation due to stigma associated with the disease. Patients also reported frequent emergency room visits in the past 12 months.
- Patients reported that current therapies provide some relief from symptoms for some patients, and that side effects and less actual control of asthma than patients think there is may result in suboptimal adherence to current therapies. The use of systemic corticosteroids is associated with short-term and long-term AEs. Patients also reported losses in productivity as a result of illness, medical appointments, and associated travel time.
- Patients are looking for drugs that can reduce asthma symptoms, reduce emergency department visits and hospitalizations, improve the ability to fight infections, and allow for higher energy levels.
- Patients expressed frustration that therapies (like omalizumab) used to treat other forms of severe asthma are ineffective for most patients with severe eosinophilic asthma, and no other comparable alternatives exist.

Details of Included Studies in the CADTH Common Drug Review Clinical Reviews for Benralizumab, Mepolizumab, and Reslizumab

Three pivotal manufacturer-sponsored double-blind RCTs were included in the CDR clinical review for benralizumab. CALIMA and SIROCCO were similarly designed studies that compared two different doses of benralizumab, administered every four weeks and every eight weeks, with placebo. ZONDA was a 28-week study that compared benralizumab every four or eight weeks with placebo. Only the every eight weeks regimen is of interest as it is the Health Canada–approved regimen. CALIMA was a 56-week study and SIROCCO lasted 48 weeks, and the full population in SIROCCO was on high-dose ICS, while CALIMA

included both high- and medium-dose ICS, the latter group added as a protocol amendment. Both studies enrolled populations with ≥ 300 cells/μL and < 300 cells/μL eosinophil counts, in a 2:1 ratio, respectively, and the primary analysis in both focused on patients in the ≥ 300 cells/μL eosinophil count group who were on high-dose ICS.

Critical appraisal issues for CALIMA and SIROCCO included the lack of an active comparator in the included studies, such as existing interleukin-5 (IL-5) inhibitors (reslizumab and mepolizumab). Only statistical comparisons made on outcomes of exacerbations, change in FEV_1, and total asthma symptom scores were controlled for multiple comparisons, while other important outcomes such as health-related quality of life and exacerbations resulting in hospitalizations and emergency room visits were not adjusted for multiplicity. The included studies all had a relatively short duration of follow-up in which to assess the longer-term safety of benralizumab. However, these limitations were not considered by CDR reviewers as major threats to the validity of the trials, and results reported are believable as the studies appear to have been reasonably well-conducted.

Critical appraisal issues for ZONDA included the lack of an active comparator, including existing IL-5 inhibitors like reslizumab and mepolizumab, and lack of adjustments for multiple statistical testing across end points other than the primary and key secondary subgroups and sensitivity analyses. ZONDA was relatively short in duration, especially for assessing exacerbations (one year minimum follow-up is preferred to accrue sufficient exacerbation events and the seasonal variability with exacerbations). Hence, there is uncertainty regarding the true benefit of benralizumab in reducing the annual rate of exacerbations in patients with chronic OCS use due to the shorter length of the trial. ZONDA was designed with a relatively small sample size compared with CALIMA and SIROCCO, which may have been because eosinophilic asthma is relatively uncommon. However, despite these limitations, there were no major threats to the validity of the trials, and the results reported (other than exacerbations) are believable as the study appeared to have been reasonably well-conducted.

Two phase III, multicenter, multinational, double-blind, placebo-controlled superiority randomized trials were included in the CDR clinical review for mepolizumab. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab SC 100 mg and mepolizumab IV 75 mg once every four weeks as adjunctive therapy in patients with severe eosinophilic asthma. In MENSA, patients had a run-in period of at least one to six weeks before being randomized in a 1:1:1 ratio to receive mepolizumab 100 mg SC, mepolizumab 75 mg IV, or placebo for 32 weeks, with treatments being administered in a double dummy fashion. Only the mepolizumab SC 100 mg once every four weeks regimen was of interest as it is the Health Canada–approved regimen. SIRIUS (N = 135) was a 24-week corticosteroid sparing study that evaluated the effect of mepolizumab SC 100 mg once every four weeks in reducing OCS use in patients with severe eosinophilic asthma. In SIRIUS, eligible patients who were currently using OCS at a dose between 5 mg and 35 mg per day went through a three- to eight-week optimization phase where OCS dose adjustments were made every week to determine the lowest effective dose of OCS before the occurrence of an exacerbation. After the optimization phase, patients were randomized in a 1:1 ratio, stratified by prior duration of OCS use (≥ 5 years and < 5 years), to receive mepolizumab 100 mg SC and placebo. One dose of study medication was administered during the four-week induction phase to allow sufficient time for patients in the mepolizumab group to decrease eosinophilic inflammation prior to OCS reduction. After the induction phase, patients entered the 16-week OCS reduction phase during which OCS doses were

gradually reduced every four weeks according to a titration schedule, before entering a four-week maintenance phase during which no more OCS dose adjustments were made.

Limitations of MENSA and SIRIUS included the relatively short durations (32 and 24 weeks, respectively) to evaluate asthma exacerbations; as mentioned, a 52-week study would have been better to assess asthma exacerbations in order to accrue sufficient numbers of events and because exacerbations fluctuate with changing seasons. Hence, there is uncertainty regarding the true benefit of mepolizumab in reducing the annual rate of exacerbations due to the shorter length of the trials. In addition, there was the potential for improved adherence to background therapy in a clinical trial setting compared with real-life as evidenced by improvements in the placebo groups, and the uncertainty regarding appropriate selection criteria to identify severe eosinophilic asthma patients. However, these critical appraisal points are not major threats to the validity of the trials, and results reported (other than exacerbations) are believable as the study appear to have been reasonably well-conducted.

A total of four double-blind RCTs were included in the CDR clinical review for reslizumab: two identical pivotal trials (Study 3082 and Study 3083) and two supporting trials (Study 3081 and Study 3084). The objective of the pivotal trials was to assess the efficacy of reslizumab versus placebo on the frequency of asthma exacerbations over a 12-month treatment period in patients with inadequately controlled asthma and elevated eosinophil levels. Patients were randomized to reslizumab (3 mg/kg IV every four weeks) or placebo. In total, 489 and 464 patients were randomized in studies 3082 and 3083, respectively. The objective of the supporting trials was to assess the efficacy of reslizumab versus placebo in terms of changes in FEV_1 (Study 3081) or change in FEV_1 relative to baseline eosinophil levels (Study 3084) over 16 weeks. In Study 3081, patients with inadequately controlled asthma and elevated eosinophil levels (N = 315) were randomized 1:1:1 to reslizumab (3 mg/kg IV every four weeks), reslizumab (0.3 mg/kg IV), or placebo. In Study 3084, patients with inadequately controlled asthma (N = 492) were randomized 4:1 to reslizumab (3 mg/kg IV every four weeks) or placebo.

Details of the CALIMA, SIROCCO, and MENSA studies are presented in Table 1, and the studies included in the CDR clinical review for reslizumab are presented in Table 2.

The inclusion criteria were similar between the SIROCCO and CALIMA (benralizumab) trials and the MENSA (mepolizumab) trial in the following criteria: age, the number of documented asthma exacerbations in the previous 12 months, pre-bronchodilator FEV_1 criteria, and documented post-bronchodilator reversibility in FEV_1 criteria. As for the exclusion criteria, the three trials were similar in excluding patients who had clinically important pulmonary disease other than asthma, were current smokers or former smokers with a smoking history of at least 10 pack years, had received any marketed (e.g., omalizumab) or investigational biologic within four months (SIROCCO and CALIMA trials) or 130 days (MENSA trial), and had a previous history of cancer in remission for less than 12 months. Studies included in the CDR clinical review for reslizumab were similar in their inclusion criteria to the MENSA, SIROCCO, and CALIMA trials in age and airway reversibility of at least 12%. As for the exclusion criteria, the three trials were similar in excluding patients who had clinically important pulmonary disease other than asthma, and were a current smoker. Trials included in the CDR clinical review for reslizumab were also similar in their inclusion criteria to the SIROCCO and CALIMA trials in having patients who had an Asthma Control Questionnaire (ACQ) score of at least 1.5 (ACQ-7 was used in trials included in the CDR clinical review for reslizumab, while ACQ-6 was used in SIROCCO and CALIMA).

The inclusion criteria were different between the SIROCCO and CALIMA (benralizumab) trials and the MENSA (mepolizumab) trial in the following criteria: the ICS dose had to be at least 500 mcg fluticasone propionate (FP) daily or equivalent in the SIROCCO and CALIMA trials versus at least 880 mcg FP daily or equivalent in MENSA. There were no inclusion criteria in SIROCCO and CALIMA for peripheral blood eosinophil count, while the criteria were at least 150 cells/µL at visit 1 or at least 300 cells/µL in the past 12 months in the MENSA trial. The ACQ was not a criterion in the MENSA trial, while it was in the SIROCCO and CALIMA trials. The trials also differed in duration as the MENSA trial was of 32 weeks duration, considerably different from the duration of the other two studies (i.e., 48 weeks in SIROCCO and 56 weeks in CALIMA). Studies included in the CDR clinical review for reslizumab were different in their inclusion criteria from MENSA, SIROCCO, and CALIMA in the following criteria: ICS dose of at least 440 mcg per day of fluticasone or equivalent, number of asthma exacerbation in the past year (at least one in the reslizumab trials versus at least two in MENSA, SIROCCO, and CALIMA), blood eosinophil count (≥ 400 cells/µL in the reslizumab trial versus at least 150 cells/µL at visit 1 or at least 300 cells/µL in past 12 months in the MENSA trial and no criteria in SIROCCO and CALIMA). They also differed in excluding patients who used a systemic immunosuppressive, immunomodulating, or other biologic drug within six months.

Table 1: Details of CALIMA, SIROCCO, and MENSA Studies

		CALIMA	SIROCCO	MENSA
Designs and Populations	**Study design**	DB RCT	DB RCT	DB RCT
	Locations	303 centres in 11 countries (Canada, US, Europe, South America, Asia)	374 centres in 17 countries (US, Mexico, Europe, South America, Australia, Asia)	119 centres in 16 countries (Canada, US, Australia, South America, Europe, Asia)
	Randomized (N)	1,306	1,205	576
	Inclusion criteria (almost similar in all three trials trials)	• Female and male aged 12 to 75 years (adolescents in Europe were not allowed to take the q.4.w. regimen) • Weight of ≥ 40 kg • Pre-bronchodilator FEV_1 of < 80% (< 90% predicted for patients 12 to 17 years of age) predicted at day of randomization visit • At least 2 documented asthma exacerbations in the 12 months prior to the date of informed consent, which required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dose of OCS • Documented post-bronchodilator reversibility in FEV_1 of ≥ 12% and > 200 mL in FEV_1 within 12 months prior to visit 1. If historical documentation was not available, reversibility had to be demonstrated and documented at visit 2		• Female and male aged at least 12 years • Weight ≥ 45 kg • Pre-bronchodilator FEV_1 of < 80% predicted (< 90% predicted for patients 12 to 17 years of age) at visit 1 • History of two or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to visit 1, despite the use of high-dose ICS • Asthma documented within past 12 months: airway reversibility of FEV_1 ≥ 12% and ≥ 200 mL or airway hyper-responsiveness or airflow variability FEV_1 ≥ 20% between two clinic visits or diurnal airflow variability PEF > 20% on ≥ 3 days

		CALIMA	SIROCCO	MENSA
	Inclusion criteria (distinct)	• Physician-diagnosed asthma requiring treatment with medium- to high-dose ICS (> 250 mcg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to visit 1 • Documented treatment with ICS and LABA for at least 3 months prior to visit 1 with or without OCS and additional asthma controllers. The ICS and LABA could be parts of a combination product or given by separate inhalers • Met ≥ 1 of the following conditions over the 7 days prior to randomization: ○ > 2 days with a daytime or nighttime symptoms score ≥ 1 ○ Rescue short-acting beta agonist use on > 2 days ○ ≥ 1 nocturnal awakening due to asthma • ACQ-6 score ≥ 1.5 at visit 1		• Have a documented requirement for regular treatment with high-dose ICS in the 12 months prior to visit 1 with or without maintenance oral OCS and require additional controller medication besides ICS; e.g., LABA, LTRA, or theophylline in the past 12 months for at least three successive months • Peripheral blood eosinophil count ≥ 150 cells/μL at visit 1 or ≥ 300 cells/μL in past 12 months
		Documented treatment with an ICS+LABA for at least 3 months prior to visit 1, with or without ICS: The ICS dose had to be ≥ 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily	Documented treatment with an ICS+LABA for at least 3 months prior to visit 1, with or without ICS: For patients 18 years of age and older, the ICS dose had to be > 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily For patients ages 12-17, the ICS dose had to be ≥ 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily	Have a documented requirement for regular treatment with high-dose ICS in the 12 months prior to visit 1 (ages ≥ 18: ≥ 880 mcg/day FP [ex-actuator] or equivalent daily; ages 12-17 ≥ 440 mcg/day FP [ex-actuator] or equivalent)
	Exclusion criteria (almost similar in all three trials trials)	• Clinically important pulmonary disease other than asthma • Current smokers or former smokers with a smoking history of ≥ 10 pack years • Receipt of any marketed (e.g., omalizumab) or investigational biologic within 4 months • Previous history of cancer in remission < 12 months		• Concurrent clinically important respiratory disease other than asthma • Current smokers or former smokers with a smoking history of ≥ 10 pack years • Use of omalizumab within 130 days • Previous history of cancer in remission < 12 months
	Exclusion criteria (distinct)	• Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent		
		Clinically significant asthma exacerbation, in the opinion of the		

		CALIMA	SIROCCO	MENSA
		investigator, including those requiring use of OCS, or an increase in maintenance dose of OCS 14 days prior to the date of informed consent		
DRUGS	**Intervention**	Benralizumab 30 mg once every 4 weeks or benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period	Benralizumab 30 mg once every 4 weeks or benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period	Mepolizumab 100 mg SC once every 4 weeks or Mepolizumab 75 mg IV once every 4 weeks
	Comparator(s)	Placebo	Placebo	Placebo
DURATION	**Phase**			
	Run-in	2 weeks minimum	2 weeks minimum	1 to 6 weeks
	Double-blind	56 weeks	48 weeks	32 weeks
	Follow-up	4 weeks (extension available [BORA study])	4 weeks (extension available [BORA study])	8 weeks
OUTCOMES	**Primary end point**	Annual asthma exacerbation rate		Frequency of asthma exacerbations requiring systemic CS and/or hospitalization and/or ED visits
NOTES	**Publications**	Fitzgerald et al., 2016[1,2]	Bleecker et al., 2016[3,4]	Ortega et al., 2014[5,6]

ACQ-5 = Asthma Control Questionnaire 5; ACQ-6 = Asthma Control Questionnaire 6; CS = corticosteroids; DB = double blind; ED = emergency department; FEV_1 = forced expiratory volume in one second; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; PEF = peak expiratory flow; q.4.w. = every eight weeks; RCT = randomized controlled trial; SC = subcutaneous.

Source: Fitzgerald et al., 2016;[1,2] Bleecker et al., 2016;[3,4] Ortega et al., 2014;[5,6] clinical study reports for CALIMA,[7] SIROCCO,[8] and MENSA.[9]

Table 2: Details of Study 3082, Study 3083, Study 3081, and Study 3084

		Study 3082	Study 3083	Study 3081	Study 3084
Designs and Populations	**Study design**	DB RCT	DB RCT	DB RCT	DB RCT
	Locations	Asia, North America, South America, Europe, South Africa (3082), Australia, and New Zealand (3082)		Europe, North America, South America, Israel	US
	Randomized (N)	489	464	315	492
	Inclusion criteria	• Female and male aged 12 to 75 years • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (including oral corticosteroids up to 10 mg prednisone or equivalent daily) at stable doses for prior 30 days • Eosinophil count of ≥ 400 cells/μL during screening period • At least one asthma exacerbation that required systemic corticosteroids (for ≥ 3 days) in the past 12 months • Airway reversibility of 12% or more with SABA • Inadequately controlled asthma (ACQ-7 score ≥ 1.5)		• Female and male aged 12 to 75 years • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (excluding oral corticosteroids) at stable doses for prior 30 days • Eosinophil count of ≥ 400 cells/μL during screening period • Airway reversibility (≥ 12% with SABA) • Inadequately controlled asthma (ACQ-7 score ≥ 1.5)	• Female and male aged 18 to 65 years • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (excluding oral corticosteroids) • Airway reversibility (≥ 12% with SABA) • Inadequately controlled asthma (ACQ-7 score ≥ 1.5)
	Exclusion criteria	• Asthma exacerbation during the screening period or 4 weeks prior to screening • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months) • Use of systemic immunosuppressive, immunomodulating, or other biologic drug within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating condition (e.g., rhinitis, GERD, uncontrolled diabetes)		• Currently using or had used systemic corticosteroids in the last 30 days • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months) • Use of systemic immunosuppressive, immunomodulating, or other biologic drug within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating condition (e.g., rhinitis, GERD, uncontrolled diabetes)	• Currently using or had used systemic corticosteroids in the last 30 days • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months) • Use of systemic immunosuppressive, immunomodulating, or other biologic drug within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating condition (e.g., rhinitis, GERD, uncontrolled diabetes)

		Study 3082	Study 3083	Study 3081	Study 3084
		• Immunodeficiency • Active or recent infection		• Immunodeficiency • Current infection	• Immunodeficiency • Current infection
Drugs	**Intervention**	Reslizumab 3 mg/kg every 4 weeks IV (13 doses)		Reslizumab 3 mg/kg every 4 weeks IV (4 doses) Reslizumab 0.3 mg/kg every 4 weeks IV	Reslizumab 3 mg/kg every 4 weeks IV (4 doses)
	Comparator(s)	Placebo every 4 weeks IV		Placebo every 4 weeks IV	Placebo every 4 weeks IV
Duration	**Phase**	III		III	III
	Screening	2 to 4 weeks		2 to 4 weeks	3 weeks
	Double-blind	52 weeks		16 weeks	16 weeks
	Follow-up	90 days		90 days	12 weeks
Outcomes	**Primary end point**	• Asthma exacerbation frequency		• Change from baseline in FEV_1	• Change from baseline in FEV_1 relative to baseline eosinophil levels
Notes	**Publications**	Castro et al., 2015[10,11]		Bjermer et al., 2016[12]	Corren et al., 2016[13]

ACQ-7 = Asthma Control Questionnaire 7; COPD = chronic obstructive pulmonary disease; DB = double blind; FEV_1 = forced expiratory volume in one second; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids; RCT = randomized controlled trial; SABA = short-acting beta agonist.

Source: Castro et al., 2015;[10,11] Bjermer et al., 2016;[12] Corren et al., 2016;[13] clinical study report.[14-17]

Details of the ZONDA and SIRIUS studies are presented in Table 3.

The inclusion criteria were similar between the ZONDA (benralizumab) trial and the SIRIUS (mepolizumab) trial in the following criteria: peripheral blood eosinophil count of ≥ 150 cells/μL at visit 1, OCS use (chronic OCS therapy for at least six continuous months directly preceding visit 1 in ZONDA versus patients with maintenance systemic corticosteroids in the six months prior to visit 1 in SIRIUS), pre-bronchodilator FEV_1 of < 80% predicted, evidence of asthma as documented by either airway reversibility, documented reversibility, airway hyper-responsiveness, or airflow variability. As for the exclusion criteria, the three trials were similar in excluding patients who had clinically important pulmonary disease other than asthma, were current smokers or former smokers with a smoking history of at least 10 pack years, and had received any marketed (e.g., omalizumab) or investigational biologic within four months (ZONDA trial) or 130 days (SIRIUS trial).

The inclusion criteria were different between the ZONDA (benralizumab) trial and SIRIUS (mepolizumab) trial in the following criteria: the documented treatment with ICS dose had to be greater than 500 mcg FP daily or equivalent for at least six continuous months preceding visit 1 in the ZONDA trial versus documented requirement for regular treatment with high-dose ICS (at least 880 mcg FP daily or equivalent) in the 12 months prior to visit 1 in MENSA. Patients had to have peripheral blood eosinophil count of 300 cells/μL in past 12 months if they did not have peripheral blood eosinophil count ≥ 150 cells/μL at visit 1 in order to be included in the SIRIUS trial, while there was no criteria for peripheral blood eosinophil count in the past 12 months in the ZONDA trial. Patients in the ZONDA trial had to have at least one documented asthma exacerbation in the previous 12 months, while there was no such criterion in the SIRIUS trial. In ZONDA, patients had to have continuous

treatment with an OCS (between 7.5 mg and 40 mg of prednisone daily), while in SIRIUS, patients were to be on regular treatment with high-dose ICS in the past six months with an additional controller medication for at least three successive months in the past 12 months. Patients had to be on regular treatment with OCS at a dose of 5 mg to 35 mg per day prednisone or equivalent.

Table 3: Details of ZONDA and SIRIUS Studies

		ZONDA	SIRIUS
Designs and Populations	**Study design**	DB RCT	DB RCT
	Locations	64 centres: 12 countries (Canada, US, Europe, South America, South Korea)	38 centres in 10 countries: Canada (3), US, Australia, Europe
	Randomized (N)	220	135
	Inclusion criteria (almost similar in both trials)	• Female and male aged 18 to 75 years • Weight of ≥ 40 kg • Peripheral blood eosinophil count of ≥ 150 cells/μL assessed by local lab at visit 1 (week 10) • Asthma requiring treatment with medium- to high-dose ICS (> 250mcg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to visit 1 • For ICS/LABA combination preparations, the highest approved maintenance dose in the local country met this ICS criterion • Chronic OCS therapy for at least 6 continuous months directly preceding visit 1 (week 10). Patients must have been on doses equivalent to 7.5 mg/day to 40 mg/day of prednisolone/prednisone at visit 1 and must have been on a stable dose for at least 2 weeks prior to randomization • Morning pre-bronchodilator FEV_1 of < 80% predicted at visit 2 • Evidence of asthma as documented by either: ○ Airway reversibility (FEV_1 ≥ 12% and 200 mL) demonstrated at visit 1 , visit 2, or visit 3 (Week -10, -8, or -6) using the Maximum Post-bronchodilator Procedure OR ○ Documented reversibility in the previous 24 months prior to Visit 1 (Week 10) OR ○ Airway hyper-responsiveness (PC20 FEV_1 methacholine concentration ≤ 8mg/mL) documented in the previous 12 months prior to planned date of randomization OR ○ Airflow variability in clinic FEV_1 ≥ 20% between	• Female and male aged at least 12 years • Weigh ≥ 45 kg • Peripheral blood eosinophil count ≥ 150 cells/μL at visit 1 or ≥ 300 cells/μL in past 12 months • Documented requirement for regular treatment with high-dose inhaled corticosteroid in the 6 months prior to visit 1 • For ICS/LABA combination preparations, the highest approved maintenance dose (for patients who are older than 18 years) or the mid-strength approved maintenance dose (for patients in the age group ages 12 to 17) in the local country will meet this ICS criterion • Patients with severe asthma and a well-documented requirement for regular treatment with maintenance systemic corticosteroids in the 6 months prior to visit 1 and using a stable oral corticosteroid dose for 4 weeks prior to visit 1. Subjects must be taking 5.0 mg/day to 35 mg/day of prednisone or equivalent at visit • Pre-bronchodilator FEV_1 of < 80% predicted (< 90% predicted for patients 12 to 17 years of age) at visit 1 • Evidence of asthma as documented by either: ○ Airway reversibility (FEV_1 ≥ 12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3 OR ○ documented in the previous 12 months OR ○ Airway hyper-responsiveness (PC20 of < 8mg/mL or PD20 of < 7.8 μmol methacholine/histamine) documented in the 12 months prior to visit 3 OR ○ Airflow variability in clinic FEV_1 ≥ 20% between two consecutive clinic visits documented in the 12 months prior to visit 3 (FEV_1 recorded during an exacerbation should not be

		ZONDA	SIRIUS
		2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV_1 recorded during an exacerbation should not be considered for this criterion) **Inclusion Criteria at Randomization** Optimized OCS dose reached at least 2 weeks prior to randomization	considered for this criteria) OR ○ Airflow variability as indicated by ≥ 20% diurnal variability in peak flow observed on 3 or more days during the optimization period **Inclusion Criteria at Randomization** Achieved a stable dose of OCS during the optimization period which is defined as 2 weeks on the same dose of oral corticosteroids prior to randomization. The optimized dose must be between 5.0 mg/day and 35 mg/day of OCS
	Inclusion criteria (distinct)	• Documented treatment with high-dose ICS (> 500 mcg fluticasone propionate dry powder formulation equivalents total daily dose) and LABA for at least 6 months prior to visit 1 (week 10) • The ICS and LABA could have been contained within a combination product or given by separate inhalers • At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent was obtained	• Have a documented requirement for regular treatment with high-dose ICS in the 12 months prior to visit 1 (ages ≥ 18: ≥ 880 mcg/day FP [ex-actuator] or equivalent daily; ages 12 to 17 ≥ 440 mcg/day FP [ex-actuator] or equivalent)
	Exclusion criteria (almost similar in all three trials trials)	• Clinically important pulmonary disease other than asthma • Current smokers or former smokers with a smoking history of ≥ 10 pack years • Receipt of any marketed (e.g., omalizumab) or investigational biologic within 4 months	• Presence of a clinically important lung condition other than asthma • Current smokers or former smokers with a smoking history of ≥ 10 pack years • Use of omalizumab within 130 days
	Exclusion criteria (distinct)	• Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior	
DRUGS	**Intervention**	Benralizumab 30 mg once every 4 weeks Benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period	Mepolizumab 100 mg SC once every 4 weeks
	Comparator(s)	Placebo	Placebo
DURATION	**Phase**		
	Run-in	8 weeks	3 to 8 weeks (optimize OCS dose)
	Double-blind	28 weeks	24 weeks (4 weeks induction, 16 weeks OCS reduction, 4 weeks maintenance)
	Follow-up	8 weeks (extension available [BORA study])	8 weeks
OUTCOMES	**Primary end point**	Percentage reduction in final OCS dose compared with baseline (visit 6), while maintaining asthma control	Per cent reduction of OCS dose during weeks 20 to 24 compared with baseline dose, while maintaining asthma control

		ZONDA	SIRIUS
NOTES	**Publications**	Nair, 2017[18,19]	Bel et al., 2014[20,21]

DB = double blind; FEV_1 = forced expiratory volume in one second; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; OCS = oral corticosteroid; RCT = randomized controlled trial; SC = subcutaneous.

Source: Nair, 2017;[18,19] Bel et al., 2014;[20,21] clinical study reports for ZONDA[22] and SIRIUS.[23]

Baseline Characteristics of Patients in the Studies Reviewed by the CADTH Common Drug Review for Benralizumab, Mepolizumab, and Reslizumab

The MENSA (mepolizumab) trial population was different than the patient population enrolled in the SIROCCO and CALIMA (benralizumab) trials with respect to prior exacerbation history at baseline. The percentages of patients with three or more exacerbations in the previous year included in the benralizumab and mepolizumab phase III exacerbation trials were 36% and 57%, respectively. Moreover, more patients in the mepolizumab trial were taking OCS at baseline in comparison with patients in the benralizumab trials (30% for mepolizumab versus 13% for benralizumab) (Table 4). Both of these factors indicated a more severe population included in the mepolizumab trial compared with that included in the benralizumab trials. The trials also differed in definition for high-dose ICS (> 500 mcg FP daily or equivalent in SIROCCO/CALIMA versus ≥ 880 mcg FP daily or equivalent in MENSA). The studies also varied in terms of duration of follow-up, ranging from 32 weeks to 56 weeks (SIROCCO: 48 weeks; CALIMA: 56 weeks; and MENSA: 32 weeks).

There were between 9% and 18% of patients across groups in CALIMA/SIROCCO identified as taking OCS at baseline as maintenance therapy. However, it is unclear whether these patients were using OCS on a chronic basis, as was the case for patients enrolled in ZONDA, or whether they were simply on short-term OCS when baseline assessments were performed. Per the protocol design, patients in both SIROCCO and CALIMA who were on daily OCS at baseline were required to be maintained on that same daily OCS regime and treated chronically with OCS for the duration of the study (48 to 56 weeks). In ZONDA, all patients were required to be on chronic OCS at baseline, and there was a run-in phase where their reliance on OCS to maintain control of their asthma was confirmed. Such a run-in phase to determine OCS use was not part of the designs of CALIMA/SIROCCO, so even if patients were taking OCS chronically, there was no way of determining whether they needed the drug to maintain asthma control, as was established in ZONDA. Similarly in MENSA, 30% of patients were identified as taking OCS at baseline as maintenance therapy. In SIRIUS, all patients had to have a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0 mg to 35 mg per day prednisone or equivalent) and used OCS in the six months prior to randomization and at a stable dose for four weeks prior to randomization. There was an OCS optimization phase in the SIRIUS trial that included a run-in phase that was intended to ensure that patients entered the double-blind treatment phase on the lowest dose of OCS that would manage their symptoms. Such a run-in phase to determine OCS use was not part of the design of MENSA, so even if patients were taking OCS chronically, there was no way of determining whether they needed the drug to maintain asthma control, as was established in SIRIUS.

Table 4: Summary of Baseline Characteristics for SIROCCO, CALIMA, and MENSA

Title	CALIMA		SIROCCO		MENSA	
	Benralizumab q.8.w. N = 441	Placebo N = 440	Benralizumab q.8.w. N = 398	Placebo N = 407	Mepolizumab 100 mg SC N = 194	Placebo N = 191
Mean (SD) age, years	49.0 (14.3)	48.8 (15.1)	47.6 (14.5)	48.7 (14.9)	51.2 (14.6)	49.2 (14.3)
Male, n (%)	168 (38.1)	176 (40.0)	146 (36.7)	138 (33.9)	78 (40.2)	84 (43.9)
Race, n (%)						
White	369 (83.7)	372 (84.5)	287 (72.1)	302 (74.2)	152 (78)	148 (77)
Asian	55 (12.5)	53 (12.0)	50 (12.6)	50 (12.3)	34 (18)	38 (20)
FEV_1 pre-BD (%PN)	57.9 (14.9)	58.0 (14.9)	56.1 (14.6)	56.6 (15.0)	56.1 (16.1)	57.8 (14.9)
Reversibility (%), mean (SD)	24.6 (22.9)	27.3 (44.7)	27.2 (24.5)	25.5 (23.1)	28.7 (26.6)	27.2 (20.3)
Median time since asthma diagnosis, years	16.81	16.22	14.38	14.17	20.5 (12.9)[a]	19.5 (14.6)[a]
Number of Exacerbations in the Last 12 Months (n [%])						
1	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0	1 (< 1)
2	287 (65.1)	288 (65.5)	252 (63.3)	244 (60.0)	74 (38)	89 (47)
≥ 3	153 (34.7)	152 (34.5)	146 (36.7)	163 (40.0)	120 (61.9)	101 (52.9)
≥ 4	60 (13.6)	59 (13.4)	67 (16.8)	87 (21.4)	72 (37)	55 (29)
≥ 5	NR	NR	NR	NR	44 (23)	33 (17)
Mean (SD)	2.7 (1.42)	2.7 (1.63)	2.8 (1.45)	3.0 (1.81)	NR	NR
ICS, n (%)	439 (99.5)	440 (100.0)	398 (100.0)	407 (100.0)	194 (100)[b]	191 (100)[b]
ICS total daily dose (mcg), mean (SD)	904.517 (NR)	863.015 (NR)	902.718 (NR)	896.100 (NR)	NR	NR
LABA, n (%)	435 (98.6)	440 (100.0)	398 (100.0)	407 (100.0)	NR	NR
ICS/LABA, n (%)	384 (87.1)	374 (85.0)	378 (95.0)	378 (92.9)	NR	NR
OCS, n (%)	44 (10.0)	41 (9.3)	71 (17.8)	68 (16.7)	58 (30)	59 (31)
baseline blood EOS count ≥ 300 cells/μL, n (% patients)	290 (65.8)	297 (67.5)	267 (67.1)	267 (65.6)	NR	NR
baseline blood EOS count < 300 cells/μL, n (% patients)	151 (34.2)	143 (32.5)	131 (32.9)	140 (34.4)	NR	NR
EOS count ≥ 150 cells/μL at screening	NR	NR	NR	NR	155 (80)	167 (87)
EOS count ≥ 300 cells/ μL in past 12 months	NR	NR	NR	NR	146 (75)	121 (63)
High-dosage ICS plus LABA with baseline blood eosinophils ≥ 300 cells/μL, n (% patients)	239 (54.2)	248 (56.4)	267 (67.1)	267 (65.6)	NR	NR
High-dosage ICS plus LABA with baseline blood eosinophils < 300 cells/μL, n (% patients)	125 (28.3)	122 (27.7)	131 (32.9)	140 (34.4)	NR	NR
Mean (SD) ACQ-6 score at baseline	2.75 (0.93)	2.69 (0.92)	2.80 (0.88)	2.87 (0.94)	2.26 (1.27)[c]	2.28 (1.19)[c]

%PN = per cent of predicted normal value; BD = bronchodilator; ACQ-6 = Asthma Control Questionnaire 6; EOS = eosinophil; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonists; NR = not reported; OCS = oral corticosteroid; q.8.w. = every eight weeks; SC = subcutaneous; SD = standard deviation.

Note: The highlighted cells indicate differences across benralizumab and mepolizumab trials.

[a] Numbers are mean (SD).

[b] High-dose ICS.

[c] Numbers are for ACQ.

Source: Fitzgerald et al., 2016;[1,2] Bleecker et al., 2016;[3,4] Ortega et al., 2014;[5,24] clinical study reports for CALIMA,[7] SIROCCO,[8] and MENSA.[9]

Patients enrolled into studies included in the CDR clinical review for reslizumab were predominately adults (95% to 100%) with mean age per treatment group ranging from 43.0 to 47.5 years (Table 5). The majority of patients were female (55% to 66%), Caucasian (65% to 85%), and had asthma on average for 18 to 26 years. In the pivotal trials for reslizumab, patients had an average of 1.9 to 2.1 asthma exacerbations in the previous year (range: 1 to 20 events); whereas, in the supporting trials, 54% to 57% of patients in Study 3081, and 38% to 42% of patients in Study 3084 had an exacerbation in the past year. The mean blood eosinophil counts were similar in studies 3082, 3083, and 3081 (range: 0.59 to 0.70 x 109 cells/L), and were lower in Study 3084 (0.28 x 109 cells/L). The total daily dose of ICS was also lower in Study 3084 (range 616 mcg to 628 mcg) than in the other three trials (757 mcg to 856 mcg).

Ongoing use of ICS was a requirement in all four reslizumab trials, with 26% to 48% of patients using an inhaler containing ICS alone or combined with a long-acting beta2 agonist (LABA) (59% to 79%). Overall, 86% of patients in Study 3082 and 82% of patients in Study 3083 were receiving an ICS with a LABA, with similar proportions between treatment groups. The percentage of patients using an ICS with a LABA was 80% and 75% in Study 3081, and 82% and 77% for Study 3084, in the placebo and reslizumab groups, respectively.

The major differences between the benralizumab trials (SIROCCO, CALIMA, and ZONDA) and reslizumab trials (Study 3082 and Study 3083) were the inclusion of predominantly eosinophilic asthma patients in the reslizumab trials with a blood eosinophil count of ≥ 400 cells/μL. The benralizumab trials included patients irrespective of baseline blood eosinophil count. Another difference across the reslizumab and benralizumab trials was the exacerbation history of the included patients. More than one-half of the patients included in the reslizumab trials had experienced ≥ 1 exacerbation within the previous year, whereas the benralizumab trials included patients with ≥ 2 exacerbations within the previous year. The benralizumab and reslizumab trials included patients with different disease severity. The benralizumab studies included patients with severe asthma, whereas the reslizumab studies included patients with moderate-to-severe asthma.

Table 5: Summary of Baseline Characteristics of Study 3082, Study 3083, Study 3081, and Study 3084

Characteristic	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 244	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 106	Placebo N = 98	Reslizumab N = 398
Age, years, mean (SD)	46.7 (14.8)	46.6 (13.8)	47.5 (13.8)	46.4 (13.8)	44.2 (14.9)	43.0 (14.4)	45.1 (13.4)	44.9 (12.0)
Adults (≥ 18 years), n (%)	237 (97)	239 (98)	228 (98)	224 (97)	100 (95)	101 (95)	98 (100)	398 (100)
Female, n (%)	161 (66)	142 (58)	150 (65)	144 (62)	62 (59)	62 (58)	54 (55)	261 (66)
Caucasian, n (%)	182 (75)	173 (71)	169 (73)	168 (72)	85 (81)	90 (85)	73 (74)	260 (65)
Number of patients with asthma exacerbation in past year, n (%)	244 (100)	245 (100)	232 (100)	231 (> 99)	57 (54)[a]	60 (57)[a]	37 (38)[b]	166 (42)[b]
Asthma exacerbations in past year, mean (SD), [median, range]	2.1 (2.3) [1 (1 to 20)]	1.9 (1.6) [1 (1 to 12)]	2.0 (1.8) [1 (1 to 12)]	1.9 (1.6) [1 (1 to 10)]	NR	NR	NR	NR

Characteristic	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 244	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 106	Placebo N = 98	Reslizumab N = 398
FEV_1, litres, mean (SD)	1.93 (0.79)	1.89 (0.73)	2.00 (0.67)	2.13 (0.78)	2.22 (0.81)	2.19 (0.79)	2.18 (0.64)	2.10 (0.70)
% predicted FEV_1, mean (SD)	65 (20)	64 (19)	68 (19)	70 (21)	71 (20)	70 (18)	67 (16)	67 (16)
Airway reversibility, %, mean (SD)	26 (18)	26 (15)	29 (24)	28 (16)	25 (16)	26 (19)	24 (14)	26 (18)
Patient-reported use of SABA in past 3 days, n (%)	188 (77)	170 (69)	181 (78)	182 (78)	81 (77)	78 (74)	76 (78)	301 (76)
Blood eosinophil count (10^9/L), mean (SD)[c]	0.62 (0.59)	0.70 (0.77)	0.69 (0.68)	0.61 (0.41)	0.60 (0.43)	0.59 (0.39)	0.28 (0.22)	0.28 (0.24)
ACQ-7 score, mean (SD)	2.8 (0.9)	2.7 (0.9)	2.6 (0.8)	2.6 (0.9)	2.5 (0.8)	2.6 (0.9)	2.6 (0.7)	2.6 (0.7)
Time since asthma diagnosis, years, mean (SD)	18.8 (14.2)	19.7 (15.2)	18.7 (13.3)	18.2 (14.4)	20.7 (14.5)	20.4 (15.6)	25.8 (16.8)	26.2 (15.7)
History of nasal polyps, n (%)	62 (25)	65 (27)	62 (27)	56 (24)	24 (23)	30 (28)	16 (16)	42 (11)
History of allergic rhinitis	145 (59)	141 (58)	144 (62)	129 (56)	72 (69)	79 (75)	82 (84)	321 (81)
Oral corticosteroid use at baseline, n (%)	40 (16)[d]	24 (10)[d]	18 (8)[e]	24 (10)[e]	–[d]	–[d]	–[d]	–[d]
Total daily dose ICS at baseline, mcg, mean (SD)	848 (442)	824 (380)	757 (274)	856 (588)	757 (371)	814 (453)	628 (224)	616 (241)
ICS total daily dose (mcg), median (range)	800.0 (200.0 to 3,200.0)	800.0 (200.0 to 2,280.0)	640.0 (160.0 to 2,000.0)	800.0 (160.0 to 7,000.0)	640.0 (320.0 to 2,400.0)	640.0 (400.0 to 3,400.0)	NR	NR
Medications for obstructive airway disease used in past 4 weeks, n (%)	242 (> 99)	241 (98)	231 (> 99)	232 (100)	105 (100)	106 (100)	98 (100)	395 (> 99)
SABA	207 (85)	193 (79)	210 (91)	211 (91)	91 (87)	94 (89)	98 (100)	376 (94)
ICS + LABA	173 (71)	184 (75)	142 (61)	142 (61)	62 (59)	70 (66)	77 (79)	305 (77)
ICS	87 (36)	84 (34)	93 (40)	92 (40)	50 (48)	43 (41)	28 (29)	102 (26)
Systemic corticosteroids	42 (17)	27 (11)	20 (9)	26 (11)	0	1 (1)	2 (2)	2 (< 1)
Leukotriene inhibitors	65 (27)	59 (24)	43 (19)	38 (16)	22 (21)	26 (25)	16 (16)	63 (16)
LABA	37 (15)	35 (14)	54 (23)	50 (22)	26 (25)	17 (16)	4 (4)	5 (1)
History of omalizumab treatment	3 (1)	1 (< 1)	5 (2)	2 (1)	0	0	0	5 (1)

ACQ-7 = Asthma Control Questionnaire 7; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; NR = not reported; SABA = short-acting beta agonist; SD = standard deviation.

[a] In Study 3081, five patients were misclassified at randomization as having an asthma exacerbation in the previous year and six patients were misclassified as not having an exacerbation.

[b] In Study 3084, five patients were misclassified at randomization as having an asthma exacerbation within the last 12 months and eight patients were misclassified as not having an asthma exacerbation.

[c] Patients were required to have at least one eosinophil count ≥ 400 cells/L during the screening period, which may or may not have occurred at the baseline assessment.

[d] Current use of systemic corticosteroids was an exclusion criteria.

Source: Castro et al., 2015;[10,11] Bjermer et al., 2016;[12] Corren et al., 2016;[13] clinical study report.[14-17]

Baseline eosinophil count varied across ZONDA and SIRIUS trials: [redacted] Additionally, the trials also varied in terms of the definition of high-dose ICS (> 500 mcg FP daily or equivalent in ZONDA versus ≥ 880 mcg FP daily or equivalent in SIRIUS), nicotine status (proportion of never smokers: 80.4% in ZONDA versus 60.5% in SIRIUS), and history of omalizumab use (11.5% in ZONDA versus 33% in SIRIUS) (Table 6).

Table 6: Summary of Baseline Characteristics for ZONDA and SIRIUS

Title	ZONDA		SIRIUS	
	Benralizumab q.8.w N = 73	Placebo N = 75	Mepolizumab 100 mg SC N = 69	Placebo N = 66
Mean (SD) age, years	52.9 (10.1)	49.9 (11.7)	49.8 (14.1)	49.9 (10.3)
Male, n (%)	26 (35.6)	27 (36.0)	25 (36)	36 (55)
Race, n (%)				
White	66 (90.4)	70 (93.3)	67 (97)	61 (92)
Asian	5 (6.8)	4 (5.3)	1 (1)	2 (3)
Mean (SD) BMI (kg/m^2)	30.24 (6.534)	28.73 (5.244)	27.8 (5.9)	29.5 (6.0)
FEV_1 pre-BD (%PN)	59.0 (17.9)	62.0 (16.5)	58.4 (17.9)	55.6 (18.3)
Reversibility (%), Mean (SD)	25.1 (19.0)	23.2 (18.0)	24.9 (19.3)	23.7 (18.6)
Median Time since asthma diagnosis, years (range)	16.34 (NR)	10.48 (NR)	17.4 (11.8)[a]	20.1 (14.4)[a]
Number of Exacerbations in the Last 12 Months (n [%])				
1	[redacted]	[redacted]	11 (16)	11 (17)
2	[redacted]	[redacted]	9 (13)	14 (21)
3	[redacted]	[redacted]	9 (13)	11 (17)
≥ 4	[redacted]	[redacted]	28 (41)	20 (30)
Mean (SD)	[redacted]	[redacted]	3.3 (3.39)	2.9 (2.76)
Nicotine Use at Study Entry (n [%])				
Never smoked	[redacted]	[redacted]	41 (59)	41 (62)
Current smoker	[redacted]	[redacted]	0	0
Former smoker	[redacted]	[redacted]	28 (41)	25 (38)
Maintenance Asthma Medications at Baseline				
ICS, n (%)	73 (100.0)	75 (100.0)	69 (100)[b]	66 (100)[b]
OCS, n (%)	73 (100)	75 (100)	69 (100)	66 (100)
OCS total daily dose (mg), mean (SD)	14.589 (7.8397)	15.080 (6.7314)	12.5[c]	15[c]
History of omalizumab treatment	[redacted]	[redacted]	23 (33)	22 (33)
Local baseline eosinophil count (cells/μL) Mean (SD)	[redacted]	[redacted]	413.0 (386.2)	347.0 (303.3)
Median Blood Eosinophils (Range) — Cells/μL				
≥ 150 cells/μL to < 300 cells/μL, n (%)	12 (16)	11 (15)	NR	NR
≥ 300 cells/μL, n (%)	61 (84)	64 (85)	NR	NR

Title	ZONDA		SIRIUS	
	Benralizumab q.8.w N = 73	Placebo N = 75	Mepolizumab 100 mg SC N = 69	Placebo N = 66
Mean (SD) ACQ-6 score at baseline	2.42 (1.21)	2.68 (0.95)	2.2 (1.3)	2.0 (1.2)

%PN = per cent of predicted normal value; ACQ-6 Asthma Control Questionnaire 6; BD = bronchodilator; BMI = body mass index; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; NR = not reported; OCS = oral corticosteroid; q.8.w. = every eight weeks; SC = subcutaneous; SD = standard deviation.

Note: The highlighted cells indicate differences across benralizumab and mepolizumab trials.

[a] Numbers are mean (SD).

[b] High-dose ICS.

[c] Median daily oral glucocorticoid dose in mg.

[c] Numbers are for ACQ-5.

Source: Nair, 2017;[18,25] Bel et al., 2014;[20,26] clinical study reports for ZONDA[22] and SIRIUS.[23]

Conclusion of the Indirect Treatment Comparisons

In the absence of head-to-head trial data for mepolizumab with omalizumab, the manufacturer conducted an ITC analysis based on a systematic review of RCTs to compare the efficacy and safety of mepolizumab with omalizumab in the treatment of patients with severe asthma. Although the ITC results suggested that mepolizumab was similarly efficacy compared with omalizumab in terms of clinically significant exacerbation, hospitalization, change in FEV_1, and with a similar safety profile, there are very serious limitations with the analysis — in part stemming from the limited number of source trials for the analysis — and a high degree of uncertainty associated with the ITC findings. Therefore, no conclusion can be drawn regarding the comparative effectiveness and safety of mepolizumab with omalizumab in the treatment of severe asthma.

Comparison of the Indications and CADTH Canadian Drug Expert Committee Recommendations of Benralizumab, Mepolizumab, and Reslizumab

Details of the indications and CDEC recommendations for benralizumab, mepolizumab, and reslizumab are presented in Table 7.

Table 7: Health Canada–Approved Indications and CADTH Canadian Drug Expert Committee Recommendations for Benralizumab, Mepolizumab, and Reslizumab

	Benralizumab	Mepolizumab	Reslizumab
Indications	As an add-on maintenance treatment of adult patients with severe eosinophilic asthma	As 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/μL (0.15 GI/L) at initiation of treatment with Nucala OR ≥ 300 cells/μL (0.3 GI/L) in the past 12 months	As an add-on maintenance treatment of adult patients with severe eosinophilic asthma who: • are inadequately controlled with medium- to high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA) and • have a blood eosinophil count of ≥ 400 cells/μL at initiation of the treatment
CDEC recommendations	Reimbursed as an add-on maintenance treatment for adult patients with severe eosinophilic asthma	Reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids (ICSs) and one or more additional asthma controller(s) (e.g., a long-acting beta agonist [LABA]), and have a blood eosinophil count of ≥ 150 cells/mcL at initiation of treatment with mepolizumab or ≥ 300 cells/mcL in the past 12 months	Reimbursed for add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose inhaled corticosteroids (ICSs) and an additional asthma controller(s) (e.g., a long-acting beta agonist [LABA]), and have a blood eosinophil count of ≥ 400 cells/μL at initiation of the treatment
Criteria	• Patient is inadequately controlled with high-dose ICSs and one or more additional asthma controller(s) (e.g., long-acting beta agonists [LABAs]), if one of the following two clinical criteria is met: ○ blood eosinophil count of ≥ 300 cells/μL AND has experienced two or more clinically significant asthma exacerbations in the past 12 months, OR ○ blood eosinophil count of ≥ 150 cells/μL AND is treated chronically with oral corticosteroids (OCSs) • Benralizumab should not be prescribed to patients who smoke • Benralizumab should not be used in combination with other biologics used to treat asthma	• Patients who have experienced two or more clinically significant asthma exacerbations in the past 12 months and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry) • Are treated with daily oral corticosteroids (OCSs)	• Patients who have experienced one or more clinically significant asthma exacerbations in the past 12 months, who have an Asthma Control Questionnaire 7 (ACQ-7) score ≥ 1.5 points, and who show reversibility (at least 12% and 200 mL) on pulmonary function tests (i.e., spirometry) • Reslizumab is not to be used in combination with other biologics for the treatment of asthma

	Benralizumab	Mepolizumab	Reslizumab
Conditions	• Patients should be managed by a physician with expertise in treating asthma • Drug plan cost of treatment not to exceed the drug plan cost of the least expensive interleukin-5 (IL-5) inhibitor reimbursed for the treatment of severe eosinophilic asthma	• Patients should be managed by a physician with expertise in treating asthma • Substantial reduction in price	• Patients should be managed by a physician with expertise in treating asthma • Reduction in price of 90%
Reasons for the recommendation	• Two multinational double-blind randomized controlled trials (RCTs), CALIMA (N = 1,306, 56 weeks) and SIROCCO (N = 1,206, 48 weeks) demonstrated that, compared with placebo, benralizumab treatment reduced the annualized exacerbation rate in patients with severe eosinophilic asthma who were not controlled on high-dose ICS + LABA. One double-blind RCT, ZONDA (N = 220; 28 weeks), which enrolled patients with severe asthma who required chronic use (at least six months) of an OCS to maintain asthma control, demonstrated that patients receiving benralizumab experienced a greater reduction in OCS dose than with placebo • No head-to-head trials have been conducted comparing benralizumab with other IL-5 inhibitors in patients with asthma. An indirect comparison (IDC) submitted by the manufacturer suggested that benralizumab is as effective and as safe as mepolizumab and omalizumab (an immunoglobulin E inhibitor), but the comparative efficacy of benralizumab versus reslizumab is unknown • At the submitted price of $3,876.92 per syringe, the incremental cost-utility ratio (ICUR) for benralizumab plus standard of care (SOC) was $1,534,803 per quality-adjusted life-year (QALY) compared with	• Evidence from two phase III, double-blind, randomized placebo-controlled trials supports the safety and efficacy of mepolizumab. In MENSA (N = 576), mepolizumab was associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo at 32 weeks in patients currently on high-dose ICS and one or more additional asthma controller(s). In SIRIUS (N = 135), mepolizumab was associated with a greater likelihood of a reduction in daily OCS dose at 24 weeks compared with placebo in patients currently on high-dose ICS and one or more additional asthma controller(s), and who were taking OCS at a dose of 5 mg/day to 35 mg/day • At the submitted price of [redacted] per vial, the CADTH Common Drug Review (CDR) estimated that mepolizumab plus standard of care (SOC) is associated with an incremental cost-effectiveness ratio (ICER) of $521,000 per quality-adjusted life-year (QALY) compared with SOC alone in the treatment of adults with severe eosinophilic asthma; therefore, mepolizumab is not considered to be cost-effective at the submitted price	• A total of four phase III, double-blind, randomized placebo-controlled trials provided evidence for the efficacy and safety of reslizumab: two identical 52-week pivotal trials (studies 3082 [N = 489] and 3083 [N = 464]) and two supporting 16-week trials (studies 3081 [N = 315] and 3084 [N = 492]). In studies 3082 and 3083, reslizumab was associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo at 52 weeks in patients currently on medium- to-high-dose ICSs with or without additional asthma controller(s) and an elevated blood eosinophil level (i.e., ≥ 400 cells/μL). The adjusted rate ratios were 0.50 (95% confidence interval [CI], 0.37 to 0.67) in Study 3082 and 0.41 (95% CI, 0.28 to 0.59) in Study 3083 for reslizumab versus placebo. However, the clinical significance was unclear for the differences observed in health-related quality of life, asthma symptoms, and pulmonary function in the pivotal trials • The manufacturer submitted a network meta-analysis (NMA) to evaluate the relative efficacy of reslizumab with mepolizumab and omalizumab in patients with severe eosinophilic asthma who would be eligible for all three therapies. CDEC identified some serious limitations in the NMA with respect to the comparison

	Benralizumab	Mepolizumab	Reslizumab
	SOC alone. At this ICUR, it is highly unlikely that benralizumab will be cost-effective at the submitted price for all patients with severe uncontrolled eosinophilic asthma. There is no evidence available that would justify a price premium for benralizumab compared with other biologic drugs used to treat severe eosinophilic asthma		between reslizumab, mepolizumab, and omalizumab and noted a high degree of uncertainty associated with its findings. Therefore, no firm conclusion could be drawn regarding the comparative effectiveness and safety of reslizumab versus other biologics in the treatment of severe eosinophilic asthma • At the submitted price of $640.00 per 10 mg/mL vial, the CADTH Common Drug Review (CDR) estimated that reslizumab plus standard of care (SOC) is associated with an incremental cost-effectiveness ratio (ICER) of $888,000 to $1,200,000 per quality-adjusted life-year (QALY) compared with SOC alone in the treatment of adults with severe eosinophilic asthma; therefore, reslizumab is not considered to be cost-effective at the submitted price

CI = confidence interval; CDEC = CADTH Common Drug Review Committee; ICS = inhaled corticosteroids; IL-5 = interleukin-5; ICUR = incremental cost-utility ratio; LABA = long-acting beta2 agonist; NMA = network meta-analysis; OCS = oral corticosteroid; RCT = randomized controlled trial; SOC = standard of care.

Source: CDEC recommendations for benralizumab,[27] reslizumab,[28] mepolizumab.[29]

Comparison of the Clinical Criteria Recommended by the CADTH Canadian Drug Expert Committee for Benralizumab, Mepolizumab, and Reslizumab

Despite their similar indication for add-on maintenance treatment of adult patients with severe eosinophilic asthma, IL-5 inhibitors indications and CDEC recommendations are based on a fairly heterogeneous evidence base. Importantly, there appear to be notable differences between CDEC recommendations for the three IL-5 inhibitors with respect to clinical criteria. Certain CDEC criteria are specified for only one product (e.g., ACQ-7 score; smoking status). Table 8 summarizes the characteristics and clinical criteria recommended by CDEC for the IL-5 inhibitors indicated for the treatment of severe eosinophilic asthma.

Table 8: Characteristics and Clinical Criteria Recommended by the CADTH Canadian Drug Expert Committee for Interleukin-5 Inhibitors

	Benralizumab Fasenra	Mepolizumab Nucala	Reslizumab Cinqair
Date of CDEC recommendation	August 21, 2018	June 16, 2016	March 22, 2017
Formulation	Subcutaneous injection	Subcutaneous injection	IV infusion
Dosage	30 mg once every 4 weeks for the first 3 doses then once every 8 weeks (fixed dose regimen)	100mg every 4 weeks (fixed dose regimen)	3mg/kg every 4 weeks (weight-adjusted therapy)
CDEC clinical criteria			
For add-on maintenance treatment of adult patients with severe eosinophilic asthma	Specified	Specified	Specified
Inadequate control with inhaled corticosteroid (ICS) and controller (i.e., long-acting beta agonists (LABA)	High-dose ICS (part of CDEC clinical criteria)	High-dose ICS (indication)	Medium- to high-dose ICS (indication)
Blood eosinophil (EOS) counts (cells/μL)	≥ 300 at initiation; OR ≥ 150 at initiation and chronic OCS treatment (CDEC clinical criteria)	≥ 150 at initiation, or ≥ 300 in the past 12 months (indication)	≥ 400 at initiation (indication)
Number of clinically significant asthma exacerbations	2 or more in the past 12 months for patients with blood EOS ≥ 300 at initiation	2 or more in the past 12 months	1 or more in the past 12 months
Show reversibility (12% or 200 mL) on pulmonary function tests (i.e., spirometry)	Not specified	Specified	Specified
Oral corticosteroid (OCS) usage	Chronic usage required if blood EOS count ≥ 150	Daily OCS required	Not specified
ACQ-7 score ≥ 1.5 points	Not specified	Not specified	Specified
Patients to be managed by physicians with expertise in treating asthma	Specified	Specified	Specified
No combination with other biologics used to treat asthma	Specified	Not specified	Specified
Should not be prescribed in patients who smoke	Specified	Not specified	Not specified

ACQ = Asthma Control Questionnaire; CDEC = CADTH Canadian Drug Expert Committee; EOS = eosinophil; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonist; OCS = oral corticosteroid.

Source: Product monographs for benralizumab,[30] reslizumab,[31] mepolizumab,[32] and CDEC recommendations for benralizumab,[27] reslizumab,[28] mepolizumab.[29]

Possible Alignment of Criteria for CADTH Canadian Drug Expert Committee Recommendations of Benralizumab, Mepolizumab, and Reslizumab

Current CDEC recommendations for benralizumab, mepolizumab, and reslizumab include unique criteria based on eosinophil levels, concomitant asthma medications, and exacerbation history, which are clinically relevant to ensure that patients eligible for therapy align with the clinical evidence supporting each therapy. Head-to-head clinical studies of these three therapies would be needed to adequately inform criteria in a specific severe eosinophilic asthma population. However, alignment may be possible for the following criteria:

Main indication: Add-on maintenance treatment of adult patients with severe eosinophilic asthma is already the same for the three drugs. However, benralizumab has a broad Health Canada label with no eosinophil level requirement, while mepolizumab and reslizumab have indications that reflect eosinophil cut-offs in the Health Canada indications. Detailed indications are presented in Table 7.

Inadequately controlled with ICSs and an additional asthma controller(s) (e.g., LABA): The CDEC recommendations for benralizumab and mepolizumab indicated that patients had to be inadequately controlled with high-dose ICSs and one or more additional asthma controller(s) (e.g., LABA). The recommendation for reslizumab indicated that patients had to be inadequately controlled with medium- to high-dose ICSs and an additional asthma controller(s) (e.g., LABA). While it is not clear from the studies included in the CDR clinical review for reslizumab the percentage of patients who were using high-dose ICS plus LABA, the clinical expert consulted on this review indicated that patients with severe eosinophilic asthma who are uncontrolled on medium-dose ICS would not step to reslizumab, but rather to high-dose ICS (in combination with another controller) based on current clinical practice in Canada. The expert noted that even though the Health Canada indication mentions that patients had to be inadequately controlled with medium- to high-dose ICSs and additional asthma controller(s) (e.g., LABA), the CDEC recommendations may be aligned for this criterion to be in patients who are inadequately controlled with high-dose ICSs and one or more additional asthma controller(s) (e.g., LABA). In addition, the Canadian Thoracic Society[33] indicated that anti-IL-5 therapies may be considered for use in spite of optimal asthma treatment, including high doses of ICS and at least one other controller.

Exacerbations: The CDEC recommendations for benralizumab and mepolizumab had a clinical criterion that patients should have experienced two or more clinically significant asthma exacerbations in the past 12 months to be eligible for treatment, while the CDEC recommendation for reslizumab indicated that patients should have experienced one or more clinically significant asthma exacerbations in the past 12 months. While the recommendation for reslizumab is in line with the clinical trials that were included in the reslizumab review, the clinical expert consulted on this review indicated that aligning the criteria for exacerbations between the three drugs is possible, where the criteria would be that patients should have experienced two or more clinically significant asthma exacerbations in the past 12 months. The clinical expert indicated in general a single exacerbation event in a 12-month period does not in and of itself indicate diminished asthma control; exposure to a rhinovirus or flu virus, or seasonal effects put most patients with

asthma at risk for exacerbation, meaning that two exacerbations in which a patient requires systemic corticosteroid is probably more suggestive that there is clinically important reduced asthma control.

Reversibility on pulmonary function tests criterion: The pivotal studies for all three anti-IL-5 drugs had reversibility in the inclusion criteria. However, the clinical expert consulted on this review indicated that the reversibility criteria are a historical trial requirement. The clinical expert also indicated that while reversibility is still used in practice to initially diagnose patients with asthma, reversibility is not necessarily sensitive enough to be used as a routine assessment of response to asthma therapies and the degree to which a patient's asthma is controlled. Evidence of reversibility in the latter situation probably implies an acute current illness where there is acutely increased inflammation that is not treated yet, or poor adherence to asthma controller medications. For the majority of asthma patients who would be eligible to receive these biologics, despite optimized controller therapy, they do not demonstrate reversibility post-bronchodilator inhalation, and some will have irreversible airway obstruction from long-term uncontrolled asthma. The clinical expert indicated that the reversibility criterion could be removed and instead a criterion added that patients have "proven asthma," which could be defined based (in part) on the patient's history that reversibility through spirometry was demonstrated. The Canadian Thoracic Society indicated that the preferred pulmonary function criterion supportive of an asthma diagnosis is spirometry showing reversible airway obstruction,[34] and that in the absence of current or historic reversibility confirming diagnosis of asthma, confirmation can be found by either spirometry pre- and post-bronchodilator or methacholine challenge test.[33]

OCS usage: Currently, the recommendations for benralizumab and mepolizumab are not aligned with respect to OCS use, but the clinical expert consulted on this review indicated that the criteria could be aligned to be patients who are treated chronically with OCS. There were no clinical trials included in the reslizumab review that assessed the efficacy of reslizumab in patients who are treated chronically with OCS or treated with daily OCS. Given the lack of evidence for reslizumab in this subgroup of patients with severe eosinophilic asthma, it would be difficult to include such criteria in the reslizumab CDEC recommendation. The clinical expert indicated that, based on the lack of data and on current practice, reslizumab should not be used in patients who are treated chronically with OCS. It is worth noting that the Canadian Thoracic Society[33] indicated that "Anti-IL-5 therapies may be considered in adults 18 years of age and over with severe eosinophilic corticosteroid-dependent asthma in an attempt to decrease or withdraw oral corticosteroids. Of note, corticosteroid sparing studies have only been undertaken with mepolizumab and benralizumab."

No combination with other biologics used to treat asthma: This criterion could be applied to all three IL-5 inhibitors given that the pivotal studies for all three anti-IL-5 drugs were not conducted in patients with biologic combination therapy.

Biologic therapy should not be prescribed in patients who smoke: This criterion could be applied to all three IL-5 inhibitors given that the pivotal studies for all three anti-IL-5 drugs were not conducted in patients who smoke. However, the clinical expert noted that current practice would not exclude treatments from patients with asthma who smoke and who require additional therapies to gain control of their disease.

Blood eosinophil count: This is one of the more heterogeneous criteria for consideration because different blood eosinophil count levels were used in the pivotal studies for the three anti-IL-5 drugs; hence, there is no evidence to align this criterion between all three drugs. In

addition, the Canadian Thoracic Society[33] concluded that "since the efficacy of these molecules is dependent upon the presence of eosinophilic inflammation, ensuring that the individual has peripheral blood eosinophil levels greater than the regulatory approved levels (which are within the normative range) and with an appropriate exacerbation history is key."

ACQ score ≥ 1.5: This criterion was only mentioned in the recommendation for reslizumab. ACQ-6 score ≥ 1.5 at visit 1 was an inclusion criterion in the pivotal trials of benralizumab and not an inclusion criterion in the pivotal trials of mepolizumab. The clinical expert consulted on this review indicated that ACQ can be used as an indicator of treatment success, and that ACQ can be added to the clinical criteria of the recommendations and as a stopping rule, especially because it is increasingly used in practice and is relatively easy to use. The ACQ (also termed the ACQ-7) is a patient-reported instrument that measures the adequacy of asthma treatment and the original instrument, the ACQ-7, consists of seven items.[35] It includes five items on symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing), one item on rescue bronchodilator use, and one item on FEV_1 as percentage of predicted FEV_1.[35] Aside from the item on FEV_1, patients fill out the questionnaire and responses are based on the past seven days. Each item is scored on a seven-point ordinal scale, ranging from zero (well controlled) to six (extremely poorly controlled).[35] The ACQ-7 score is calculated as the mean score, with all items weighted equally and therefore also ranges from zero to six with higher scores indicating worse asthma control.[35] There are two versions of the ACQ-6; one that excludes the FEV_1 item and one that excludes the item on bronchodilator use.[36] The ACQ-5 omits both the FEV_1 item and the item on bronchodilator use.[36] A more detailed description of ACQ is provided in Appendix 2. The clinical expert did not recommend one version of ACQ over another, but indicted that if reversibility is removed from the clinical criteria (where reversibility at entry indicates that patients are not well controlled), then using a more objective control measure such as ACQ could be a reasonable alternative. The clinical expert also indicated that it is not difficult for patients to achieve a score of 1.5 on the ACQ, where a score of 1.5 is in the range of uncontrolled.

Of note, none of the CDEC recommendations have criteria for treatment discontinuation for patients who do not respond adequately to anti-IL-5 therapy. The Institut national d'excellence en santé et services sociaux (INESSS) has recently introduced asthma control and treatment discontinuation criteria for IL-5 inhibitors. Assessment of asthma control using the ACQ, Asthma Control Test, St. George's Respiratory Questionnaire, or Asthma Quality of Life Questionnaire is recommended by INESSS.[37,38] INESSS has also recently provided the following guidance regarding the duration of initial and subsequent authorizations for benralizumab[37] and mepolizumab:[38]

- The maximum duration of the initial authorization is eight months. At eight months, treating physicians need to assess if patients respond, or if therapy needs to be discontinued.
- Proof of clinical benefits are to be demonstrated using one of these questionnaires:
  - reduction of ≥ 0.5 points of ACQ score; or
  - increase of ≥ 3 points of Asthma Control Test score; or
  - reduction of ≥ 4 points of St. George's Respiratory Questionnaire score; or
  - increase of ≥ 0.5 point of Asthma Quality of Life Questionnaire score.
- If patients respond at eight months, the second request will be authorized for a maximum of 12 months.

- For subsequent requests, physicians will need to demonstrate:
  - that clinical benefits are maintained using one of the previously mentioned questionnaires; or
  - a reduction in the annual number of exacerbations (i.e., requiring the use of a systemic corticosteroid or an increase in dosage in case of chronic use).
- Subsequent requests will be authorized for a maximum duration of 12 months.

Details about the recommendation on these IL-5 inhibitors by INESSS and other health technology assessment review recommendations can be found in Appendix 3.

Potential Place in Therapy[1]

Most patients in Canada with asthma can be managed with a combination of non-pharmacologic strategies (e.g., education and environmental control) and pharmacologic strategies (e.g., ICS). A second controller, such as LABA, is typically added for patients who remain uncontrolled and then, if needed, the dose of ICS is increased. Not all patients achieve asthma control, in part, due to the presence of differing asthma phenotypes.[39] Severe eosinophilic asthma is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum despite conventional asthma therapy, and it affects 5% to 10% of all asthma patients.[40] The prevalence of uncontrolled severe eosinophilic asthma is likely lower. Patients with severe uncontrolled asthma drive the majority of asthma health care costs. Biological drugs targeting allergic or non-allergic eosinophilic airway inflammation, such as benralizumab, mepolizumab, and reslizumab, are effective at achieving asthma control.[42]

Ensuring patients are adherent with inhaled therapies, stop smoking, and eliminate (or at least minimize) environmental exposures (e.g., pets or occupation) are key to achieving asthma control and impact any the effectiveness of any additional therapies, including anti-IL-5 therapies. Evidence of elevated eosinophils is required for patients to be eligible to receive reslizumab or other anti-IL-5 therapies. Peripheral eosinophil levels are easily measured and at a minimum, patients should meet peripheral eosinophil levels per the product monographs for each anti-IL-5 therapy before initiating therapy.[43] There is a role for direct measurement of airway eosinophilic inflammation to help guide initiation of therapy; however, the optimal cut-off values to guide these treatments remain uncertain.

Conclusions

While current CDEC recommendations for benralizumab, mepolizumab, and reslizumab include unique criteria based on eosinophil levels, concomitant asthma medications, and exacerbation history, which are clinically relevant to ensure that patients eligible for therapy align with the clinical evidence supporting each therapy, there is evidence to support alignment for certain criteria such as ICS dose, number of exacerbations, reversibility, combination with other biologics, patients who smoke, and ACQ. There is no evidence to support aligning the recommendations for all three IL-5 inhibitors on blood eosinophil count and OCS usage.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Appendix 1: Patient Group Input

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, the Ontario Lung Association (OLA) and Asthma Canada, provided input for this summary.

OLA is a charitable organization that assists and empowers persons living with or caring for others with lung disease, including asthma. OLA provides programs and services to patients and health care providers, invests in lung research, and advocates for improved policies on lung health. OLA works alongside nine other provincial lung associations and the Canadian Lung Association. OLA has received funding in the past two years from several pharmaceutical companies, including GlaxoSmithKline Inc., AstraZeneca Canada Inc., and Teva Canada Innovation. The funding received by the OLA from GlaxoSmithKline Inc. in the past two years was in excess of $50,000.

Asthma Canada is a nationally registered charitable organization that provides support to all Canadians affected by asthma. It aims to advocate for people living with asthma and respiratory allergies. Asthma Canada has received funding in the past two years from several pharmaceutical companies, including AstraZeneca Canada Inc., Teva Canada Innovation, and GlaxoSmithKline Inc. The funding received by Asthma Canada from GlaxoSmithKline Inc. in the past two years was in excess of $50,000.

2. Condition-Related Information

The information provided from OLA was obtained from two phone interviews with patients living with severe asthma and 91 online surveys completed by people living with a chronic lung condition and/or their caregivers. Of the 91 online surveys completed, nine were completed by patients living with a diagnosis of asthma or severe asthma. A certified respiratory educator also provided input. The information provided from Asthma Canada was obtained through consultation with Asthma Canada's Scientific and Medical Advisory Committee.

According to information provided from OLA, the symptoms and challenges that patients experience as a result of asthma are shortness of breath, fatigue, coughing (with or without mucus), wheezing, difficulty fighting infections, and weight loss. Patients also indicated that asthma greatly impacts their physical and leisure activities, and to a lesser extent, their work, ability to travel, and ability to socialize. Patients indicated that the aspects of asthma that are most important to control for people living with it are shortness of breath, coughing, and fatigue. Patients would also like better control with wheezing and an increased ability to fight infections.

3. Current Therapy-Related Information

Treatments tried by those who completed the OLA survey and were interviewed included budesonide/formoterol (Symbicort), salbutamol (Ventolin), budesonide (Pulmicort), terbutaline (Bricanyl), benralizumab (Fasenra), fluticasone furoate/umeclidinium/vilanterol (Trelegy), tiotropium (Spiriva), prednisone, and montelukast (Singulair). Mometasone nasal spray (Nasonex), cetirizine (Reactine), and other antihistamines are used for allergies as needed. Patients indicated that current treatments do provide some relief for fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection, but patients indicated that they want to experience greater assistance with managing all of these

symptoms. The side effects indicated from using the previously mentioned drugs include hoarse voice, dry mouth, increased mucus, low energy, appetite loss, impact on mood, and feeling shaky. One patient had concerns over an increased heart rate from daily inhaler use. Some patients indicated that the cost burden affected their lives, as does the time required to travel to health care settings, the time required off work for these appointments, and the changes to their daily routine to accommodate treatment. One respondent indicated that if their drug plan did not provide coverage, they would not be able to afford the medications.

4. Expectations About the Drug Being Reviewed

Patients who completed the OLA survey indicated that they want treatments that would reduce shortness of breath, reduce coughing, reduce fatigue, and improve appetite. They would like an increased ability to fight infections and to have a higher energy level. Ideally, patients would experience an improved quality of life and improved lung function. The three most commonly mentioned things that are evaluated when considering new therapies are administration of medication, side effects, and cost burden. None of the responders had experience with mepolizumab.

5. Additional Information

Asthma Canada indicated that it supports the alignment of criteria for mepolizumab, reslizumab, and benralizumab, and views this as an opportunity to address problematic issues such the reversibility criteria (to be removed from the clinical criteria), the age indication (to include as broad an age range as possible), and patchwork access across the provinces. Asthma Canada also indicated that nonresponders should be taken off the medications within four to six months so that the medication is not used too long if there is no benefit, and that patients who smoke should not be excluded given that smokers were excluded from studies on all asthma medications available and are not prevented from using inhalers on that basis. In addition, Asthma Canada also indicated that while inclusion criteria can be simplified (if not aligned), it is important to preserve choice for patients and prescribing physicians, especially as there has been evidence of patients failing on one biologic and then responding to another.

Appendix 2: Description of the Asthma Control Questionnaire

Aim

To summarize the validity of the following outcome measures:

- Asthma Control Questionnaire (ACQ)
- Asthma Control Questionnaire 6 (ACQ-6)
- Asthma Control Questionnaire 5 (ACQ-5).

Findings

Table 9: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
ACQ (also termed the ACQ-7)	ACQ is a patient-reported tool to assess asthma control in patient ≥ 6 years of age. It is comprised of the following 7 questions, of which the mean of the results is the overall score (0 indicates well-controlled asthma and 6 indicates extremely poorly controlled asthma): • daytime symptoms • nighttime awakening/symptoms • activity limitation • rescue treatment requirements (use of SABA) • lung function (FEV_1) • shortness of breath • wheezing.	Yes	0.5	Juniper 2001,[44] Juniper 2005,[36] Wyrwich 2011[45]
ACQ-6	ACQ-6 is a shortened version of the original 7-item ACQ. It is a patient-reported questionnaire for assessing the adequacy of asthma treatment. There are two versions of the ACQ-6; one which excludes the FEV_1 item and one which excludes the item on bronchodilator use.	Yes	0.5	
ACQ-5	ACQ-5 is a shortened version of the original 7-item ACQ measure. This patient-reported assessment of the adequacy of asthma treatment includes items relating exclusively to patient symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing within the past week); items relating to rescue bronchodilator use and FEV_1% of predicted normal, which are part of the original ACQ, are excluded from the ACQ-5. All items are scored on a 7-point scale, which ranges from 0 (indicating good control) to 6 (poor control). The overall score is the mean of all questions, with a high score indicating poor control.	Yes	0.5	

ACQ = Asthma Control Questionnaire; ACQ-5 = Asthma Control Questionnaire 5; ACQ-6 = Asthma Control Questionnaire 6; ACQ-7 = Asthma Control Questionnaire 7; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; SABA = short-acting beta agonist.

The ACQ (also termed the ACQ-7) is a patient-reported instrument that measures the adequacy of asthma treatment and the original instrument, the ACQ-7, consists of seven items.[35] It includes five items on symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing), one item on rescue bronchodilator use, and one item on forced expiratory volume in one second (FEV_1) as percentage of predicted FEV_1.[35] Aside from the item on FEV_1, patients fill out the questionnaire and responses are based on the past seven days. Each item is scored on a seven-point ordinal scale, ranging from zero (well controlled) to six (extremely poorly controlled).[35] The ACQ-7 score is calculated as the mean score with all items weighted equally and therefore also ranges from zero to six with higher scores indicating worse asthma control.[35]

There are two versions of the ACQ-6; one that excludes the FEV_1 item and one that excludes the item on bronchodilator use.[36] The ACQ-5 omits both the FEV_1 item and the item on bronchodilator use.[36]

In a study of 50 adults with symptomatic asthma, convergent validity of the ACQ-7 was assessed and a positive association with the Asthma Quality of Life Questionnaire (AQLQ) was demonstrated (Pearson correlation coefficient [*r*] = 0.76).[35] Although high scores represent poorly controlled asthma in the ACQ and no impairment from asthma in the AQLQ, the convention used to assess construct validity was that positive correlation coefficients indicated the association between the two measures was consistent with validity. The change in ACQ-7 and the change in AQLQ were also associated with each other in 36 patients with unstable asthma (Pearson correlation coefficient = 0.73).[35] The predicted range of strengths of association for both comparisons was 0.4 to 0.8.[35] In the same study, acceptable (≥ 0.7[46]) test-retest reliability of the ACQ-7 was demonstrated in 36 patients whose asthma was stable between clinic visits (intraclass correlation coefficient [ICC] = 0.90).[35] The ACQ-7 was also responsive to change in the patients with unstable asthma (mean change of 0.73, standard deviation = 0.54, $P < 0.0001$).[35]

Validation and agreement across the shortened versions of the ACQ (ACQ-5 and ACQ-6) has also been investigated.[36,44,45] In a reanalysis of the aforementioned ACQ-7 validation study, all three shortened versions of the ACQ had strong associations with the AQLQ (Pearson correlation coefficients ranging from 0.77 to 0.85) and acceptable test-retest reliability (ICCs of 0.89 to 0.90).[44] Responsiveness in patients with unstable asthma for the shortened versions were similar with that for the full version.[44] These findings were corroborated by two subsequent validation studies, which were based on samples from a 26-week randomized controlled trial (RCT, N = 552) and a post hoc analysis of two large RCTs (N = 737 and N = 772).[36,45] In the 26-week RCT in 552 adults with asthma requiring inhaled steroids, the ACQ-6 omitting the FEV_1 item had acceptable (≥ 0.7[46]) internal consistency reliability (Cronbach's alpha = 0.98), acceptable test-retest reliability (ICC = 0.82), and a strong positive association with the mini AQLQ (Pearson correlation coefficient = 0.76).[36] The minimal clinically important distances (MCIDs) for all versions of the ACQ were found by regressing the changes in ACQ score on changes in mini AQLQ score using a geometric mean regression model.[36] Using an MCID of 0.5 for the mini AQLQ, the results indicated an MCID of approximately 0.5 for all versions of the ACQ.[36] However, it is not clear how the MCID for the mini AQLQ was determined.[47] A separate study determined the MCID for the ACQ-7 to be 0.53 using an anchor-based approach with a global rating, though the conference abstract in which it is cited was not available at the time of this review.[48] Studies in pediatric patients with asthma have found an MCID of 0.63 for the ACQ-6 using an anchor-based approach with global rating of change,[49] an MCID of 0.375 for the ACQ-7

using a distribution-based approach,[50] and MCIDs ranging from 0.4 to 0.5 for the ACQ-7 using an anchor-based approach.[50] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator for “well controlled” and “not well controlled” asthma patients.[51]

A systematic review of the use of the ACQ in trials of commonly used asthma drugs showed that out of 11 studies using the ACQ, none demonstrated a between-groups difference in mean change in ACQ score exceeding the 0.5.[52] The authors suggested that ACQ results should be presented as a responder rate comparison.[52]

Appendix 3: Other Health Technology Assessment Review Recommendations

Table 10: Health Technology Assessment Agencies

Agency (Region)	Recommendation
NICE (United Kingdom)	
Benralizumab[53]	NF **Note:** Benralizumab for treating severe asthma [ID1129] The guidance is In development [GID-TA10192] and is expected to be published on December 19, 2018 https://www.nice.org.uk/guidance/indevelopment/gid-ta10192
Mepolizumab[54]	1. Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if: • the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and • the person has agreed to and followed the optimised standard treatment plan and ○ has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or ○ has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and • the company provides the drug with the discount agreed in the patient access scheme. 2. At 12 months of treatment: • stop mepolizumab if the asthma has not responded adequately or • continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: • at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or • a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. https://www.nice.org.uk/guidance/ta431/chapter/1-Recommendations
Reslizumab[55]	1. Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if: • the blood eosinophil count has been recorded as 400 cells per microlitre or more • the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months and • the company provides reslizumab with the discount agreed in the patient access scheme. 2. At 12 months: • stop reslizumab if the asthma has not responded adequately or • continue reslizumab if the asthma has responded adequately and assess response each year. An adequate response is defined as: • a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or • a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. https://www.nice.org.uk/guidance/ta479/chapter/1-Recommendations
SMC (Scotland)	
Benralizumab	NF
Mepolizumab[56]	Mepolizumab is accepted for restricted use within NHS Scotland. SMC restriction: patients who have eosinophils of at least 150 cells per microlitre (0.15 x 10^9/L) at initiation of treatment and have had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with oral corticosteroids. https://www.scottishmedicines.org.uk/medicines-advice/mepolizumab-nucala-fullsubmission-114916/
Reslizumab[57]	reslizumab is not recommended for use within NHS Scotland. https://www.scottishmedicines.org.uk/medicines-advice/reslizumab-cinqaero-resubmission-123317/

Agency (Region)	Recommendation	
PBAC (Australia)		
Benralizumab[58]	RES (March 2018)	
	Treatment phase:	Initial treatment
	Treatment criteria:	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.
	Clinical criteria:	Patient must be under the care of the same physician for at least 6 months, OR Patient must have been diagnosed by a multidisciplinary severe asthma clinic team AND Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV_1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV_1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days, AND Patient must have a duration of asthma of at least 1 year, AND Patient must have forced expiratory volume (FEV_1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months, AND Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months, AND Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab or mepolizumab.
	Population criteria:	Patient must be aged 12 years or older.
	Prescriber Instructions:	Optimised asthma therapy includes: (i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated; AND (ii) treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated. The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND (b) while receiving optimised asthma therapy in the past 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe

Agency (Region)	Recommendation	
		asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) assessment of the patient must be made at time of application for treatment (to establish baseline score) and again around 24 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. A patient who fails to respond to a course of PBS-subsidised benralizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with benralizumab, mepolizumab or omalizumab within 6 months of the date on which treatment was ceased. A multidisciplinary severe asthma clinic team comprises of: • A respiratory physician; and • A pharmacist, nurse or asthma educator. Benralizumab may not be used concurrently with mepolizumab or omalizumab or within 6 months of each other. A patient is required to have ceased treatment with mepolizumab or omalizumab for 6 months prior to initiating treatment with benralizumab. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/benralizumab-restrictions-psd-march-2018.pdf
	Treatment phase: Treatment criteria: Clinical criteria: Population criteria: Prescriber Instructions:	Continuing treatment Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. Patient must have demonstrated or sustained an adequate response to PBS subsidised treatment with this drug, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS subsidised omalizumab or mepolizumab. Patient must be aged 12 years or older. An adequate response to benralizumab treatment is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ 5) score of at least 0.5 from baseline, OR (b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ 5 score from baseline. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/benralizumab-restrictions-psd-march-2018.pdf
Mepolizumab[58]	Listed	
	Treatment phase: Treatment criteria: Clinical criteria:	Initial treatment Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. Patient must be under the care of the same physician for at least 6 months, OR Patient must have been diagnosed by a multidisciplinary severe asthma clinic team AND Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the

Agency (Region)	Recommendation	
		management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV_1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV_1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days, AND Patient must have a duration of asthma of at least 1 year, AND Patient must have forced expiratory volume (FEV_1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months, AND Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months, AND Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab or benralizumab.
	Population criteria:	Patient must be aged 12 years or older.
	Prescriber Instructions:	Optimised asthma therapy includes: (i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated; AND (ii) treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated. The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND (b) while receiving optimised asthma therapy in the past 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) assessment of the patient must be made at time of application for treatment (to establish baseline score) and again around 26 to 30 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. A patient who fails to respond to a course of PBS-subsidised mepolizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with mepolizumab, benralizumab or omalizumab within 6 months of the date on which treatment was ceased. A multidisciplinary severe asthma clinic team comprises of: • A respiratory physician; and

Agency (Region)	Recommendation	
		• A pharmacist, nurse or asthma educator. Mepolizumab may not be used concurrently with benralizumab or omalizumab, or within 6 months of each other. A patient is required to have ceased treatment with benralizumab or omalizumab for 6 months prior to initiating treatment with mepolizumab. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/benralizumab-restrictions-psd-march-2018.pdf
	Treatment phase: Treatment criteria: Clinical criteria: Population criteria: Prescriber Instructions:	Continuing treatment Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. Patient must have demonstrated or sustained an adequate response to PBS subsidised treatment with this drug, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS subsidised benralizumab or omalizumab. Patient must be aged 12 years or older. An adequate response to benralizumab treatment is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ 5) score of at least 0.5 from baseline, OR (b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ 5 score from baseline. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/benralizumab-restrictions-psd-march-2018.pdf
Reslizumab	NF	
PHARMAC (New Zealand)		
Benralizumab	NF	
Mepolizumab[59,60]	Listed The Committee recommended mepolizumab be funded for patients with severe refractory eosinophilic asthma, using the Special Authority criteria as recommended by the Respiratory Subcommittee, with a high priority. Special Authority for Subsidy – Severe eosinophilic asthma Initial application – respiratory physician. Approvals valid for 12 months for applications meeting the following criteria: 1. Patient must be aged 12 years or older, and 2. Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist, and 3. Conditions that mimic asthma e.g. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and 4. Patient has a blood eosinophil count of > 500 cells/μL in the last 6 weeks, and 5. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus long acting beta-2 agonist, unless contraindicated or not tolerated, and 6. Either: • Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral steroids; or	

Agency (Region)	Recommendation
	• Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months 7. Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment. Renewal – (Severe eosinophilic asthma) only from a respiratory physician. Approvals valid for 24 months for applications meeting the following criteria: Both: 1. An increase in the Asthma Control Test (ACT) score of at least 5 from baseline, and 2. Either: • Exacerbations have been reduced from baseline by 50% as a result of treatment with mepolizumab, or • Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control https://www.pharmac.govt.nz/assets/ptac-respiratory-subcommittee-minutes-2017-08.pdf
Reslizumab	NF
INESSS (Quebec)	
Benralizumab[37]	recommends that the Minister list Fasenra on the lists of medications for the treatment of eosinophilic asthma if the following condition is complied with and according to the recognized indication for the proposed payment. Criteria 1. for the treatment of severe eosinophilic asthma in adults: • who have a blood eosinophil concentration of at least 300 cells/microliter (0.30×10^9/l) when initiating treatment with benralizumab, or who had this concentration before initiating treatment with another drug targeting interleukin-5 (IL-5); and • whose symptoms are not controlled despite optimal treatment. Optimal therapy is defined as the use of an inhaled corticosteroid at a dose equivalent to 1000 mcg of fluticasone propionate, a long-acting β2 agonist, and the testing of a leukotriene receptor antagonist from an antimuscarinic long inhalation action or theophylline; and • having had at least two exacerbations in the last year, requiring the use of a systemic corticosteroid or an increase in the dose of the systemic corticosteroid in patients who receive it continuously. The physician must provide the number of exacerbations in the last year, as defined above, and the result to one of the following questionnaires: • Asthma Control Questionnaire (ACQ); or • Asthma Control Test (ACT); or • St George's Respiratory Questionnaire (SGRQ); or • Asthma Quality of Life Questionnaire (AQLQ). The initial authorization is for a maximum of 8 months. In the second request, the physician must provide the data to demonstrate the beneficial effects of the treatment: • a decrease of 0.5 points or more in ACQ; or • an increase of 3 points or more in ACT; or • a decrease of 4 points or more in the SGRQ; or

Agency (Region)	Recommendation
	• an increase of 0.5 points or more at the AQLQ. The second application will be allowed for a maximum of 12 months. In subsequent requests, the physician must provide proof of the maintenance of beneficial effects on one of the questionnaires mentioned above, or a reduction in the number of annual exacerbations, as defined above. Requests for further treatment are allowed for a maximum of 12 months. Authorizations are given at a maximum dose of 30 mg every 8 weeks. or 2. for the treatment of severe asthma requiring the use of an oral corticosteroid continuously for at least 3 months, in adults with eosinophilic blood concentrations of at least 150 cells/microliter (0.15 x 10^9/l) at the time of initiation of treatment with benralizumab, or who had this concentration before initiating treatment with another drug targeting interleukin-5 (IL-5). The initial authorization is for a maximum of 8 months. On the second request, the physician must confirm a decrease in the maintenance dose of corticosteroid equivalent to 10 mg or more of prednisone or at least 50% of that before starting treatment with benralizumab. The second application will be allowed for a maximum of 12 months. Upon subsequent requests, the physician must confirm that maintenance dose reduction of oral corticosteroid is maintained. Requests for further treatment are allowed for a maximum of 12 months. Authorizations are given at a maximum dose of 30 mg every 8 weeks. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Septembre_2018/Fasenra_2018_08.pdf
Mepolizumab[38]	recommends to the Minister to modify the recognized indication for the payment of Nucala for the treatment of eosinophilic asthma, if the following condition is met and according to the recognized indication for the proposed payment. Criteria 1. for the treatment of severe eosinophilic asthma in adults with or having: • a blood concentration of eosinophils of at least 150 cells / microliter (0.15 x 10^9/l) at the time of initiating treatment with an interleukin-5 (IL-5) targeting agent, or at least 300 cells / microliter (0.3 x 10^9/l) in the 12 months prior to treatment with an IL-5 targeting agent; and • whose symptoms are not controlled despite optimal treatment. Optimal therapy is defined as the use of an inhaled corticosteroid at a dose equivalent to 1000 mcg of fluticasone propionate, a long-acting β2 agonist, and the testing of a leukotriene receptor antagonist from an antimuscarinic long inhalation action or theophylline; and • having had at least two exacerbations in the last year, requiring the use of a systemic corticosteroid or an increase in the dose of the systemic corticosteroid in patients who receive it continuously. The physician must provide the number of exacerbations in the last year, as defined above, and the result to one of the following questionnaires: • Asthma Control Questionnaire (ACQ); or • Asthma Control Test (ACT);

Agency (Region)	Recommendation
	or • St George's Respiratory Questionnaire (SGRQ); or • Asthma Quality of Life Questionnaire (AQLQ). The initial authorization is for a maximum of 8 months. In the second request, the physician must provide the data to demonstrate the beneficial effects of the treatment: • a decrease of 0.5 points or more in ACQ; or • an increase of 3 points or more in ACT; or • a decrease of 4 points or more in the SGRQ; or • an increase of 0.5 points or more at the AQLQ. The second application will be allowed for a maximum of 12 months. In subsequent requests, the physician must provide proof of the maintenance of beneficial effects on one of the questionnaires mentioned above, or a reduction in the number of annual exacerbations, as defined above. Requests for further treatment are allowed for a maximum of 12 months. Authorizations are given at a maximum dose of 30 mg every 8 weeks. or 2. for the treatment of severe asthma requiring the use of an oral corticosteroid continuously for at least 3 months, in adults with eosinophilic blood concentrations of at least 150 cells / microliter (0.15 x 10^9/l) at the time of initiating treatment with an agent targeting interleukin-5 (IL-5) or at least 300 cells / microliter (0.3 x 10^9/l) in the 12 months prior to treatment with an agent targeting interleukin-5 (IL-5). The initial authorization is for a maximum of 8 months. On the second request, the physician must confirm a decrease in the maintenance dose of corticosteroid equivalent to 10 mg or more of prednisone or at least 50% of that before starting treatment with benralizumab. The second application will be allowed for a maximum of 12 months. Upon subsequent requests, the physician must confirm that maintenance dose reduction of oral corticosteroid is maintained. Requests for further treatment are allowed for a maximum of 12 months. Authorizations are given at a maximum dose of 30 mg every 8 weeks. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Septembre_2018/Nucala_RevCritere_2018_08.pdf
Reslizumab[61]	not to include Cinqair on the lists of drugs for the treatment of severe eosinophilic asthma, as it does not meet the criterion of therapeutic https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Juin_2017/Cinqair_2017_06.pdf
HAS (France)	

Agency (Region)	Recommendation
Benralizumab	NF
Mepolizumab[62]	• It must be prescribed by a physician experienced in the diagnosis and management of severe refractory eosinophilic asthma. • It is reserved for adults with severe refractory eosinophilic asthma defined by a blood eosinophil level ≥ 300/µL in the last twelve months AND at least one of the 2 following criteria: ○ 2 episodes of asthmatic exacerbations having required treatment with oral corticosteroids (> 3 days each) in the last 12 months despite a basic treatment combining high-dose inhaled corticosteroids and a long-acting bronchodilator (LABA) (step 4/5 GINA); ○ a treatment with oral corticosteroid therapy for at least 6 months during the last 12 months. https://www.has-sante.fr/portail/upload/docs/application/pdf/2016-12/nucala_summary_ct14895.pdf
Reslizumab	NF

HAS = Haute Autorité de Santé; INESSS = Institut national d'excellence en santé et services sociaux; NF = No recommendation found for the indication of interest; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not recommended; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RES = use restricted by criteria/conditions; REC = recommended for use; SMC = Scottish Medicine Consortium.

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