CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Review Report

INDACATEROL/MOMETASONE FUROATE (ATECTURA BREEZHALER)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airway disease

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CADTH

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

BIA	budget impact analysis
COPD	chronic obstructive pulmonary disease
ED	emergency department
EQ VAS	EuroQol Visual Analogue Scale
GINA	Global Initiative for Asthma
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
LABA	long-acting beta2-agonist
MF	mometasone furoate
OCS	oral corticosteroid
ODB	Ontario Drug Benefit
QALY	quality-adjusted life-year
QMF	indacaterol/mometasone furoate
QoL	quality of life
S/F	salmeterol/fluticasone propionate
VAS	visual analogue scale
WTP	willingness-to-pay

Executive Summary

The executive summary comprises two tables (Table 1: Submitted for Review and Table 2: Summary of Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	QMF (Atectura Breezhaler), available as inhalation powder (hard capsules) (150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg) delivered via the Breezhaler device
Submitted price	QMF 150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg = $1.94 per capsule for all strengths
Indication	Once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. QMF should be prescribed for patients not adequately controlled on a long-term asthma control medication such as ICS or whose disease severity clearly warrants treatment with both a LABA and an ICS.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	May 6, 2020
Reimbursement request	As per indication
Sponsor	Novartis Pharmaceuticals Canada Inc.
Submission history	Previously reviewed: No

ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist; QMF = indacaterol acetate/mometasone furoate.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis
Target population(s)	Adults and adolescents 12 years of age and older with reversible obstructive airways disease that is not adequately controlled on a long-term asthma control medication such as ICS or whose disease severity clearly warrants treatment with both a LABA and an ICS
Treatments	QMF 150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg
Comparators	MF 200 mcg, 400 mcg, 800 mcg S/F 50 mcg/500 mcg
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs, exacerbations (moderate, severe)
Time horizon	Lifetime (50 years)
Key data source	PALLADIUM trial (QMF 150 mcg/160 mcg,150 mcg/320 mcg), QUARTZ trial (QMF 150 mcg/80 mcg)
Submitted results for base case	The sponsor submitted two base-case analyses. **Based on PALLADIUM trial (sequential):** • QMF 150 mcg/160 mcg vs. MF 400 mcg = ICER $5,673 per QALY • QMF 150 mcg/320 mcg was extendedly dominated by MF 400 mcg and QMF 150 mcg/160 mcg **Based on QUARTZ trial:** • QMF 150 mcg/80 mcg vs. MF 200 mcg = ICER $15,344 per QALY
Key limitations	• Uncertainty exists regarding the cost-effectiveness of QMF relative to other currently available ICS/LABA fixed-dose combination treatments. Owing to a lack of comparative evidence, only one of several currently available ICS/LABA treatments (S/F) was considered in the sponsor's submission. MF, a monotherapy ICS, was not considered to be a relevant comparator for the cost-effectiveness

Component	Description
	analysis as QMF is intended for patients for whom an ICS/LABA combination treatment is appropriate. • The price of S/F was based on the brand name version, despite the availability of a generic. • Health utility estimates were treatment specific and were based on the visual analogue scale, which does not incorporate preferences for health states. Uncertainty exists regarding whether there is a utility benefit associated with QMF, whether it is maintained beyond the clinical trial duration, and whether it is applicable to Canadian patients. • There is limited evidence about the duration of the treatment effect. The sponsor assumed that the clinical effects of QMF and comparators on asthma exacerbations observed in 12-week and 52-week trials would be maintained for 50 years. • The impact of adverse events on the cost-effectiveness estimates is uncertain, as adverse events were not explicitly considered in the sponsor's model. Adverse events were commonly experienced by participants in the PALLADIUM trial, with 5% to 8% experiencing a serious adverse event. • The cost-effectiveness of QMF among adolescents is highly uncertain. The sponsor's analyses were based on adult patients, and the clinical trials on which the effectiveness and utility values are based enrolled predominantly adult patients. Clinical responsiveness and health care utilization may vary between adolescents and adults, thus affecting cost-effectiveness estimates.
CADTH reanalysis results	• In the CADTH reanalysis, the price of S/F was corrected, QMF was compared to medium-dose S/F (250 mcg/50 mcg), and utility values were assumed to be equivalent across treatments. CADTH was unable to address the uncertainty associated with the long-term clinical effectiveness of QMF or the impact of adverse events on the ICER. • Based on CADTH reanalyses: ○ QMF 150 mcg/160 mcg is not cost-effective at a $50,000 WTP threshold, with an ICER of $1,083,197 per QALY vs. medium-dose S/F ○ QMF 150 mcg/320 mcg is cost-saving for individuals requiring high-dose ICS/LABA, providing similar health outcomes at a lower cost than high-dose S/F ○ QMF 150 mcg/80 mcg is not cost-effective at a $50,000 WTP threshold for individuals requiring low-dose ICS/LABA, with an ICER of $2,298,606 per QALY vs. low-dose S/F.

ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LY = life-year; MF = mometasone furoate; QALY= quality-adjusted life-year; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate; vs. = versus; WTP = willingness to pay.

Note: "Extendedly dominated" refers to a treatment having a higher ICER when compared to both the previous and next most-effective treatment.

Conclusions

Based on CADTH reanalyses, for patients who require low-dose or medium-dose combinations of inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) (ICS/LABA), less expensive options are available that could achieve very similar health outcomes to indacaterol/mometasone furoate (QMF). Therefore, for QMF to be considered cost-effective in these patients, QMF should be priced no more than the least expensive available alternative. For patients who require a high-dose ICS/LABA combination, QMF 150 mcg/ 320 mcg is less expensive than all alternative comparators and is likely associated with similar health outcomes, making it cost-effective in these patients.

CADTH was unable to address the cost-effectiveness of QMF relative to other currently available ICS/LABA treatments due to lack of evidence. In CADTH's reanalyses, it was assumed that current ICS/LABA options, at similar doses, would achieve similar health outcomes. There is no clinical evidence to support a price premium for QMF above similarly dosed ICS/LABA combinations. The cost-effectiveness of QMF among adolescents is uncertain as the sponsor's analysis reflects a predominately adult population and no subgroup analysis was performed.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

Patient input was received from the Lung Health Foundation and Asthma Canada in response to the joint call by CADTH for patient input into the reviews of QMF (Atectura Breezhaler) and indacaterol /glycopyrronium /mometasone furoate (Enerzair Breezhaler). These patient groups provided input intended for use in both reviews. The Lung Health Foundation gathered information via interviews with three patients with asthma (May 2020), while Asthma Canada gathered information through interviews and an online survey involving 24 patients and 200 patients with asthma, respectively, as part of a 2014 report.[1] Asthma Canada conducted an additional online survey in 2020 (192 respondents) to provide additional information for the current evidence submission.

Both patient groups described the challenges associated with asthma, including wheezing, coughing, shortness of breath, a tight sensation in the chest, fatigue, and difficulty fighting colds and infections. Such symptoms occur in a chronic manner and also as acute severe attacks (exacerbations). Patients also described how asthma limits their daily activities and exercise, as well as affects their performance at work or school and causes missed days of school or work. Patients described visits to the emergency department (ED) because of asthma, with many respondents having more than one ED visit and/or hospital admission in the previous year because of their asthma.

Both patient groups expressed a desire for improved quality of life (QoL) and lung function. Key outcomes that patients would like addressed include a reduction of shortness of breath, coughing, and fatigue, as well as improved ability to control day-to-day symptoms, an improved ability to exercise (higher energy level), and an increased ability to fight colds and infections.

Asthma Canada reported that asthma management in current Canadian clinical practice involves the avoidance of triggers that worsen symptoms, the use of a long-term controller medication on an ongoing basis, and the use of a short-acting reliever medication for exacerbations or severe symptoms. Patients reported treatment experience with Symbicort, Ventolin, Advair, Spiriva, Prednisone, and Singulair, which provided some relief for their symptoms. Reported side effects of medications experienced by patients include dry mouth or thrush, hoarseness, appetite loss, impact on mood, difficulty sleeping, increased heart rate, and "*feeling jittery/shaky*."

Patients highlighted having to make trade-offs between side effects and asthma control. For patients with severe asthma, side effects may regularly disrupt their activity levels, including social and work interactions, and can lead to a lower health-related QoL. When considering trying a new medication, patients described reflecting on how the medication is administered, the side effects, and the financial burden. In terms of administration, patients agreed that being able to combine medications into one device safely would be beneficial to them. Based on the 2014 report that was associated with the 2020 Asthma Canada survey,[1] more than half of respondents do not regularly take their long-term controller medication, and Asthma Canada described how patients often believe that they do not need to continue taking their medications when they are asymptomatic. Other reasons for non-compliance include lack of efficacy (continued exacerbations), side effects, and financial burden.

Several of these aspects were addressed in the sponsor's model:

- The clinical effectiveness of asthma treatments was based on the rate of asthma exacerbations (moderate, severe). Those who experienced a severe exacerbation were assumed to have lower health-related QoL for four weeks. The sponsor assumed that moderate exacerbations would not affect patients' QoL.
- Loss of workplace productivity due to absenteeism was considered via scenario analyses.

Some aspects were not addressed in the sponsor's model and could not be addressed by CADTH owing to structural or data limitations:

- adverse events related to asthma treatment
- treatment compliance or adherence
- improvements in lung function.

Economic Review

The current review is for QMF (Atectura Breezhaler) for adults and adolescents 12 years of age and older with reversible obstructive airways disease whose asthma is not controlled on a long-term asthma control medication, such as an ICS, or whose disease severity warrants treatment with both a LABA and an ICS.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing QMF, a once-daily fixed-dose combination inhaler including an ICS (mometasone furoate [MF]) and LABA (indacaterol).[2] QMF is indicated as a once-daily maintenance treatment for adults and adolescents 12 years of age and older with reversible obstructive airways disease whose asthma is not controlled on a long-term asthma control medication such as ICS or whose disease severity warrants treatment with both a LABA and an ICS.[3] Two base-case analyses were undertaken by the sponsor based on the PALLADIUM and QUARTZ trials,[4, 5] which included different comparators. The modelled populations were consistent with these trials and aligned with the funding request. No subgroup analyses were performed.

Three strengths of QMF are available: 150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg. The recommended dosage for patients who require a low dose of ICS is once-daily inhalation of one 150 mcg/80 mcg capsule. For patients who require a medium dose or high dose of ICS, the recommended dosage is once-daily inhalation of one 150 mcg/160 mcg or 150 mcg/320 mcg capsule. The annual cost of QMF (for all strengths) is $707 based on a unit cost of $1.94 per capsule. Comparators to QMF in the sponsor's submission were a dual ICS/LABA combination treatment (salmeterol/fluticasone propionate [S/F]; Advair Diskus) and an ICS monotherapy (MF).

The clinical outcomes in the sponsor's model were quality-adjusted life-years (QALYs), life-years, and number of asthma exacerbations (severe, moderate, total). The sponsor adopted a lifetime horizon (50 years) using four-week cycles and undertook the analysis from the

perspective of the publicly funded health care payer. Costs and clinical outcomes were discounted at a rate of 1.5% per year.

Model Structure

The economic analysis was conducted using a Markov model in Microsoft Excel. The model consisted of two health states: day-to-day symptoms and death (the absorbing health state) (Appendix 3). Patients in the day-to-day symptoms state could experience moderate or severe exacerbations. For patients who experience a severe exacerbation, 5% were assumed to require admission to hospital while 5% were assumed to visit an ED (but not be admitted to hospital) and 90% were assumed to manage their exacerbation by use of an oral corticosteroid (OCS) burst. Severe exacerbations were further assumed to require treatment with prednisone (five days if the patient required an OCS burst or ED visit, or 30 days if admitted to hospital). Moderate exacerbations were managed with three days of prednisone treatment.

Model Inputs

The sponsor submitted two base-case analyses, one modelled on the PALLIDIUM trial[5] and the other on the QUARTZ trial.[4] Both trials were phase III multi-centre, randomized controlled trials, but utilized different treatment durations, comparators, and inclusion criteria. PALLADIUM compared QMF 150 mcg/160 mcg and QMF 150 mcg/320 mcg to MF 400 mcg, MF 800 mcg, and S/F 50 mcg/500 mcg. Participants enrolled were "*aged ≥12 and ≤75 years with a diagnosis of asthma for at least one year prior to screening and who were symptomatic despite the use of medium/high dose ICS and/or low dose LABA/ICS (i.e., GINA step ≥ 3)*," and participants received treatment for 52 weeks. The mean age of participants in PALLADIUM was 48 years, with 58% being female participants. The QUARTZ trial compared QMF 150 mcg/80 mcg with MF 200 mcg and included participants "*aged ≥12 and ≤75 years with a diagnosis of asthma for at least 3 months and who were symptomatic despite treatment with low dose ICS (i.e., GINA Steps 2-3)*." Participants received treatment for 12 weeks. The mean age in QUARTZ was 45.6 years, with 61% of participants being female.

The clinical efficacy of QMF as well as the comparators in terms of asthma exacerbations was obtained from the PALLADIUM trial (QMF 150 mcg/320 mcg, 150 mcg/160 mcg) and the QUARTZ trial (QMF 150 mcg/80 mcg).[4, 5] In the clinical trials, severe exacerbations were defined as the aggravation of asthma symptoms that required systemic corticosteroids for at least three consecutive days and/or required an ED visit or hospitalization, or that resulted in death due to asthma.[4, 5] In the pharmacoeconomic submission, the rate of severe exacerbations was directly incorporated from the trials while the rate of moderate exacerbations was calculated by subtracting the rate of moderate exacerbations from the total rate of exacerbations. The observed effect of treatment on exacerbations was assumed to be maintained over the model time horizon (50 years), with a starting cohort age of 48 years (PALLADIUM) or 46 years (QUARTZ). A subgroup analysis of adolescents aged 12 to 18 years was not performed. Mortality among patients with asthma was assumed to be equivalent to the Statistics Canada age- and gender-specific general population mortality rates. No adverse events were explicitly included in the sponsor's economic evaluation and discontinuation from treatment was not included in the sponsor's base-case analysis.

The sponsor states that health state utility values for the day-to-day symptom state were derived from the EuroQoL 5-Dimensions estimates from the PALLADIUM and QUARTZ trials.[4, 5] Disutilities related to exacerbations that required either hospital admission or an

OCS burst were obtained from a 2007 study involving 112 patients in the UK with moderate to severe asthma, in which disutility values were based on a subset of five patients who were hospitalized (for hospitalization disutility) or 22 patients who required an OCS burst.[6] The sponsor assumed that disutility related to ED visits would be equal to that associated with an OCS burst (OCS = –0.1, ED visit = –0.1, and hospitalization = –0.2) and were assumed to be experienced for the four-week cycle in which the exacerbation was experienced. No disutility was associated with moderate exacerbation.

The economic model included drug costs, as well as exacerbation-related costs to the health care system (i.e., unscheduled visits to a general practitioner, ED visits, general hospital ward visits, general hospital outpatient visits, nurse educator visits, and days of prednisone use). The price of QMF was based on the sponsor's submitted price,[2] and the price of S/F and MF were obtained from the Ontario Drug Benefit (ODB) Formulary.[7] The sponsor based the price of S/F on the ODB list price for brand name S/F (Advair Diskus). Exacerbation-related use of health care resources was based on clinical expert opinion, and costs were obtained from the Ontario Schedule of Benefits for Physician Services[8] and the Ontario Case Costing Initiative[9] for physician and hospital admission or ED visit costs, respectively. All costs were presented in 2020 Canadian dollars and costs obtained from other years were inflated to 2020 Canadian dollars.

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 1,000 probabilistic iterations, for which findings are presented as follows. The sponsor performed two base-case analyses[10] on the basis of the PALLADIUM and QUARTZ trials. Additional details pertaining to the sponsor's submission are available in Appendix 3.

Base-Case Results

The sponsor's base-case results based on PALLADIUM are presented in Table 3. Compared with MF 400 mcg, QMF 150 mcg/160 mcg was associated with an incremental cost-effectiveness ratio (ICER) of $5,673 per QALY. All other treatments were dominated or subject to extended dominance through a combination of other treatments. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, QMF 150 mcg/160 mcg and QMF 150 mcg/320 mcg have a 49.3% and 39.1% probability of being cost-effective, respectively.

Table 3: Summary of the Sponsor's Economic Evaluation Results in PALLADIUM Study

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
MF 400 mcg	15,379	20.84	—
QMF 150 mcg /320 mcg	20,282	21.61	Extendedly dominated
QMF 150 mcg /160 mcg	20,284	21.71	5,673 vs. MF 400 mcg
MF 800 mcg	27,184	21.15	Dominated
S/F 50 mcg/500 mcg	36,836	21.50	Dominated

ICER = incremental cost-effectiveness ratio; MF = mometasone furoate, QALY = quality-adjusted life-year; QMF = indacaterol/mometasone furoate, S/F = salmeterol/fluticasone propionate; vs. = versus.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

Source: Sponsor's Pharmacoeconomic Submission.[10]

The sponsor's base-case results based on QUARTZ are presented in Table 4. Compared with MF 200, QMF 150 mcg/80 mcg was associated with an ICER of $15,344. At a WTP threshold of $50,000 per QALY, QMF 150 mcg/80 mcg has a 72.3% probability of being cost-effective.

Table 4: Summary of the Sponsor's Economic Evaluation Results in QUARTZ Study

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. MF 200 mcg ($/QALY)
MF 200 mcg	9,581	–	21.78	–	–
QMF 150 mcg/80 mcg	20,773	11,192	22.51	0.73	15,344

ICER = incremental cost-effectiveness ratio; MF = mometasone furoate, QALY = quality-adjusted life-year; QMF = indacaterol/mometasone furoate; vs. = versus.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

Source: Sponsor's Pharmacoeconomic Submission.[10]

Sensitivity and Scenario Analysis Results

The sponsor conducted several sensitivity and scenario analyses. These included varying the time horizon (i.e., 10 years), varying the discount rate for costs and outcomes (0% and 3%), taking a societal perspective (i.e., including productivity costs), incorporating treatment discontinuation, and varying the source of clinical effectiveness data. In all scenarios based on the PALLADIUM trial, QMF 150 mcg/160 mcg remained the most cost-effective option at a $50,000 WTP threshold, except when productivity costs were included. In this scenario, QMF 150 mcg/160 mcg had an ICER of $164,388 when compared to QMF 150 mcg/320 mcg; all other treatment options remained dominated. In scenario analyses based on the QUARTZ trial, QMF remained the most cost-effective treatment at a $50,000 per QALY threshold for all analyses.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **The cost-effectiveness of QMF among adolescents is uncertain.** QMF is indicated for patients aged 12 years and older;[3] however, the sponsor's pharmacoeconomic submission was based on the PALLADIUM and QUARTZ trials,[4, 5] which had mean ages of 48 years and 46 years, respectively, and enrolled relatively few participants aged 12 to 17 years (PALLADIUM = 4.8%; QUARTZ = 8.0%). The clinical response by adolescents and adults may differ. Among adults in the PALLADIUM trial, there was a statistically significant difference in forced expiratory volume in one second between QMF 150 mcg/320 mcg and MF 800 mcg; however, this association was not observed among adolescents.[5] The clinical expert consulted by CADTH further indicated that health care utilization by those with severe asthma exacerbations may differ between adolescents and adults. Further, the sponsor's model assumed a starting age of 46 years to 48 years and no subgroup analyses were provided in an adolescent population. The cost-effectiveness of QMF among adolescents is thus unknown.
- **Appropriate comparators were omitted.** The Global Initiative for Asthma (GINA) guidelines[11] recommend dual ICS/LABA therapy as the preferred approach for patients not adequately controlled with an ICS and who require the addition of LABA (moderate to severe asthma; GINA step ≥ 3). Many ICS/LABAs are approved for use in Canada (Table 8). The sponsor submitted an indirect treatment comparison report that conducted a feasibility analysis to assess the viability of doing a network meta-analysis for indirect treatment comparisons to compare QMF to other ICS/LABA treatments; however, it was deemed not feasible owing to heterogeneity in terms of study

population, study treatment duration, and outcome definitions, as well as a lack of common comparators. The clinical effectiveness and cost-effectiveness of QMF relative to other available ICS/LABA treatments is thus uncertain.

The sponsor submitted two base-case analyses, based on direct evidence from the PALLADIUM trial, which compared medium-dose and high-dose QMF (150 mcg/160 mcg and 150 mcg/320 mcg) to high-dose S/F and medium-dose and high-dose MF, and from the QUARTZ trial, which compared low-dose QMF (150 mcg/80 mcg) to low-dose ICS. The clinical expert consulted by CADTH indicated that few patients would initiate an ICS/LABA treatment after failing a low-dose ICS; rather, patients would be more likely to progress to a medium-dose or high-dose ICS before a LABA is added. Thus, CADTH's base-case and scenario analyses were performed using PALLADIUM only.

- In the CADTH base case, CADTH compared medium-dose and high-dose QMF (150 mcg/160 mcg and 150 mcg/320 mcg) to medium-dose S/F. Based on GINA guidelines and the sponsor's own assessment, medium-dose ICS/LABA is a relevant comparator for a significant number of asthma patients.[11] CADTH's base-case reanalysis was thus based on medium-dose ICS/LABA as the comparator dose. This required the assumption that medium-dose S/F has equal effectiveness to high-dose S/F, which was deemed reasonable by the clinical expert. Further, a lack of additional benefit in increasing ICS dose has been demonstrated.[12] As there is a lack of direct or indirect evidence, this is the most reasonable assumption CADTH could impose to allow the cost-effectiveness of QMF to be determined. Given that low-dose ICS/LABA and high-dose ICS/LABA remain viable comparators, the cost-effectiveness of QMF versus these alterative options was explored as scenario analyses. Given that CADTH had to assume the efficacy between these ICS/LABA doses was equivalent, it was felt comparing them all in a single sequential analysis would not provide any additional insight.
- In scenario analyses, CADTH compared low-dose QMF (150 mcg/80 mcg) versus low-dose S/F, and high-dose QMF (150 mcg /320 mcg) versus high-dose S/F. This required the assumption that, for patients who require low-dose ICS/LABA treatment, a clinician would choose from among available low-dose ICS/LABA treatments. Similarly, for patients who require a high-dose ICS/LABA treatment, CADTH assumed that clinicians would choose from among available high-dose treatments. This further requires the assumption that low-dose, medium-dose, and high-dose QMF have similar clinical effectiveness (in terms of asthma exacerbations and health-related QoL). In this scenario analysis, for patients who require a low-dose ICS/LABA treatment, QMF 150 mcg/80 mcg was associated with an ICER of $2,298,606 per QALY versus low-dose S/F. In the scenario comparing high-dose QMF to high-dose S/F, QMF 150 mcg/320 mcg was dominant over high-dose S/F. CADTH cannot comment on the cost-effectiveness of different doses between brands.

- **Inappropriate comparator price**. In the sponsor's submission, the cost of S/F was based on the price of the brand name drug, despite the availability of a generic version. CADTH deemed that the appropriate comparator price should be based on the generic version of S/F.
  - In the reanalysis of the sponsor's submission, as well as in CADTH's base-case and scenario analyses, the generic price of S/F was used.
- **Uncertainty regarding differences in utilities across treatments.** For QMF 150 mcg/160 mcg and 150 mcg/320 mcg, the sponsor incorporated health state utility values for day-to-day asthma symptoms based on EuroQol Visual Analogue Scale (EQ VAS) data from the PALLADIUM trial;[5] these utility values were treatment specific. For QMF 150 mcg/80 mcg, the sponsor's submission states that utilities were based on EuroQol 5-Dimensions 5-Levels values from the QUARTZ trial. CADTH was unable to verify this statement, as EuroQoL 5-Dimensions was not included as a study outcome in the QUARTZ clinical study report.[4] Neither PALLADIUM nor QUARTZ included Canadian trial sites.

- The utility values included in the sponsor's submission from both trials were based on the last estimates taken from the trial. In PALLADIUM, treatment was received for 52 weeks, while the treatment period was 12 weeks in the QUARTZ trial. The sponsor assumed that QoL measured at the end of the trial would be permanent, lasting for the entire 50-year analysis horizon. This assumption is not supported by evidence and, given that asthma patients can step up or step down treatment, it is highly unlikely. Estimates at the end of the study also reflect participants who completed the trial and do not capture those who withdrew or who did not complete the assessment, potentially biasing the estimates.
- The differences in visual analogue scale (VAS) estimates between treatments were small at the end of the treatment period in PALLADIUM. When baseline differences between groups were considered (change from baseline), the differences in VAS estimates between treatments were even smaller; however, these estimates were inappropriately not considered by the sponsor. In PALLADIUM, the end-of-trial VAS values for QMF 150 mcg/160 mcg and 150 mcg/320 mcg were higher than for S/F ([redacted]); however, the increase from baseline was greater for S/F than for QMF 150 mcg/320 mcg. Further, the upper and lower limits for the distribution of health utility values included in the sponsor's probabilistic analysis were arbitrary (calculated as ± 5% of the mean) and do not reflect the full range of possible values. Utility estimates based on data from the PALLADIUM trial were mean EQ VAS estimates. EQ VAS assesses participants' self-rated (global) health status by use of a 100-point VAS, ranging from "best possible health state" to "worst possible health state" on the day of assessment. EQ VAS estimates do not incorporate preferences for health state and, as such, are not considered optimal for cost-effectiveness analyses.
    - It is uncertain as to whether there is a utility benefit associated with QMF, whether it is maintained past the end of the observation period, and whether the utilities reflect the preferences of Canadian patients. In the CADTH clinical review, there was no statistically significant difference in asthma-related QoL or moderate or severe asthma exacerbations between QMF and ICS/LABA treatment, thus providing evidence that there would be no expected utility differences between treatments, especially ones that lasted for the remainder of the patient's life. In CADTH's reanalysis, equal utility values were applied for each intervention and comparator. In a scenario analysis, CADTH explored the impact of sponsor-provided utility values applied that lasted only for the duration of the PALLADIUM trial (52 weeks).
- **Uncertainty regarding long-term clinical effectiveness.** Participants in PALLADIUM and QUARTZ received treatment for 52 weeks and 12 weeks, respectively. In the sponsor's pharmacoeconomic submission, the impact of QMF relative to other comparators on asthma exacerbations were consistent over the 50-year analysis horizon. Potential waning of treatment effect over time was not considered in the sponsor's model. Over time, patients who do not respond to therapy would likely step up treatment, meaning that differences captured at the end of trial would likely not be permanent for the rest of the patient's life in many cases. The short treatment duration is of particular concern for the QUARTZ trial, as the clinical expert consulted by CADTH indicated that the clinical effectiveness of asthma therapies should be evaluated over at least a one-year period in clinical trials in order to capture seasonal variation in asthma exacerbations.
    - It is uncertain whether the effect of QMF on asthma exacerbations is maintained beyond the duration of the clinical trials.
- **Impact of adverse events is uncertain.** The pharmacoeconomic analysis submitted by the sponsor did not incorporate costs to the health care system or decreased participant QoL owing to adverse events, which may affect total costs and QALYs. The sponsor's submission stated that this was owing to the low incidence of adverse events and the "*potential impact on the analysis*." The clinical expert consulted by CADTH indicated that assuming a low incidence of adverse events was unreasonable, particularly for high-

dose ICS treatments. The long-term use of high-dose ICS is associated with adverse events including pharyngitis, dysphonia, reflex cough, bronchospasm, oropharyngeal candidiasis, suppressed hypothalamic-pituitary-adrenal axis function, adrenal crisis, reduced bone mineral density, bone fractures, osteoporosis, skin thinning and bruising, cataracts, and glaucoma.[13]

As noted in the clinical review, adverse events were commonly reported in the clinical trials. In the 52-week PALLADIUM trial, adverse events were experienced by 65% to 72% of participants across treatment arms, with 5% to 8% experiencing a serious adverse event. In the 12-week QUARTZ trial, adverse events were reported for 32% to 38% of participants, with 1% to 2% experiencing a serious adverse event. In the stakeholder feedback received from the Lung Health Foundation and Asthma Canada, adverse events were of concern to patients, who described how adverse events contribute to lower health-related QoL. Because the sponsor's submission did not include costs related to treating such adverse events or decrements in health-related QoL, the impact of adverse events on cost-effectiveness is uncertain.

- Due to structural limitations, CADTH was unable to model the effects of adverse events.

Additional limitations were identified, but were not considered to be key limitations:

- **Overestimation of clinical benefit.** Clinical effectiveness in the sponsor's submission was characterized by the rates of moderate and severe asthma exacerbations, which it states were based on data from the PALLADIUM and QUARTZ trials. CADTH identified several discrepancies between the exacerbation rates in the pharmacoeconomic submission and the clinical study reports for each trial.[4, 5] For example, in the PALLADIUM trial,[5] the annualized rate of total exacerbations includes mild, moderate, and severe exacerbations; however, in the pharmacoeconomic submission, the sponsor calculated the rate of moderate exacerbations by subtracting the severe rate from the total rate (i.e., without accounting for mild exacerbations). As a result, the value included in the model for moderate exacerbation includes mild exacerbations and overestimates the number of moderate exacerbations averted. This discrepancy was found to affect QMF as well as the comparator treatments and would not be expected to substantially affect costs or QALY estimates because moderate exacerbations were associated with minor costs and no disutility.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 5).

Table 5: Key Assumptions of the Submitted Economic Evaluation — Not Noted as Limitations to the Submission

Sponsor's key assumption	CADTH comment
Patients were assumed to stay on the same dose and formulation for their lifetime.	Unreasonable. The clinical expert that CADTH consulted, as well as the GINA guidelines,[11] indicated that treatment response should be periodically reviewed and treatment dose reassessed in light of patients' responses in terms of symptom control and risk of future exacerbations and side effects. Once asthma control has been achieved and maintained for 2 to 3 months, treatment may be stepped down to find the minimum treatment dose that controls both symptoms and exacerbations.[11] Further, the clinical expert indicated that patients with suboptimal asthma control may be interested in trying new drug formulations as they become available.
Patients with asthma were considered to be at minimal risk of increased mortality compared to the general population.	Reasonable. The clinical expert that CADTH consulted indicated that this assumption was reasonable. Further, as there was no observed difference in mortality between QMF and the comparator treatments in the clinical trials, any difference in overall mortality would be expected to have a minimal effect on the ICER. The GINA guidelines note, however, that the risk of asthma-related death may be increased by

Sponsor's key assumption	CADTH comment
	admission to hospital or emergency care visits in the past year, as well as by poor adherence to asthma medications.[11]
Resource utilization was based on medical expert opinion.	Uncertain. The resource utilization estimates incorporated into the sponsor's submission were based on the sponsor's consultation with a Canadian medical estimate. The clinical expert that CADTH consulted indicated that these estimates were not in keeping with current Canadian clinical practice. In particular, the sponsor assumed that patients admitted to hospital for a severe exacerbation would receive 30 days of prednisone treatment, whereas current Canadian practice is up to 10 days. Further, the sponsor assumed that admission to hospital would not be associated with an ED visit, which is not in keeping with current practice.
The duration of disutility (i.e., lower health-related quality of life) associated with severe asthma exacerbations was assumed to be equal to the cycle length (4 weeks).	Reasonable. The clinical expert that CADTH consulted indicated that patients may experience decrements in health for 4 to 6 weeks following a severe asthma exacerbation.
For patients with a severe exacerbation, 90% would require an OCS burst, 5% would visit an ED, and 5% would be admitted to hospital.	Uncertain. The clinical expert that CADTH consulted indicated that patients with asthma are rarely admitted to hospital in Canada and that contemporary Canadian data would be required to verify this assumption. The sponsor's assumptions were based on non-Canadian studies from 2005 to 2015.[14-16] The clinical expert further indicated that the management of severe exacerbations may differ between adult and adolescent patients.
Moderate exacerbations would be treated with prednisone for 3 days only (i.e., no additional costs related to health care resource use)	Uncertain. The clinical expert that CADTH consulted indicated that patients would likely receive 5 days of prednisone (50 mg per day), and the GINA guidelines state that short-course OCS may last up to 7 days (40 mg per day to 50 mg per day).[11] Patients may require a visit to a health care provider to obtain an OCS prescription if no asthma action plan is in place. The clinical expert indicated that about 20% to 30% of patients may have such a plan. For the remaining patients, a visit or call with a health care provider would be required to obtain a prednisone prescription. GINA guidelines further recommend that patients who self-manage an exacerbation should see their health care provider to review their symptom control and risk factors for exacerbations, and to identify potential causes of the exacerbation. Patients who experience more than 1 to 2 exacerbations per year despite following GINA step 4 to step 5 therapy should further be referred to a specialist centre for assessment.[11]

ED = emergency department; ICER = incremental cost-effectiveness ratio; GINA = Global Initiative for Asthma; OCS = oral corticosteroid; QMF = indacaterol/mometasone furoate.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model and are summarized in Table 6. Due to structural or data limitations, CADTH was unable to address the impact of adverse events and the duration of treatment effect. In CADTH's base case, relevant comparators were considered to be ICS/LABA fixed-dose combination treatments.

Table 6: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
Corrected S/F cost	Cost of S/F was based on the brand name product	Cost of S/F was based on the generic product
Changes to derive the CADTH base case		
1. Revised comparator	High-dose S/F	Medium-dose S/F
2. Assumed no difference in utilities across treatments	Utilities were based on end-of-treatment EQ VAS estimates	No difference in utilities across treatments
CADTH base case	—	Reanalysis 1 and reanalysis 2

EQ VAS = EuroQol Visual Analogue Scale; S/F = salmeterol/fluticasone propionate.

CADTH's base-case results are presented in Table 7. Additional reanalyses and results are presented in Table 12.

In CADTH's base case, S/F is the least costly treatment ($17,964) and provides 21.49 QALYs over a 50-year time horizon. QMF 150 mcg/320 mcg is associated with an incremental cost of $2,317, with a minimal incremental increase in QALYs (0.002). In the sequential analysis, S/F is the preferred option if a decision-maker's WTP is below $1,083,197 per QALY. QMF 150 mcg/160 mcg is the preferred option if the WTP is more than $1,083,197 per QALY (Table 7). QMF 150 mcg/320 mcg was extendedly dominated by S/F and QMF 150 mcg/160 mcg. At a WTP of $100,000 per QALY and $50,000 per QALY, 0% of simulations resulted in QMF 150 mcg/160 mcg being cost-effective. In 50% of iterations, QMF was dominated, producing lower health outcomes at a higher cost relative to S/F 50 mcg/250 mcg. This shows that it is unlikely that QMF would provide incremental health gains, which aligns with the clinical evidence that shows there were no evidenced statistical differences in exacerbations or utilities for QMF versus S/F.

Table 7: Summary of the Results of the CADTH Reanalyses

Drug	Total costs ($)	Total QALYs	ICER vs. S/F 250 mcg/50 mcg ($/QALY)	Sequential ICER ($/QALY)
CADTH base case				
S/F 50 mcg/250 mcg[a]	17,964	21.49408	—	—
QMF 150 mcg/320 mcg	20,281	21.49617	1,108,521	Extendedly dominated through S/F 50 mcg/250 mcg and QMF 150 mcg/160 mcg
QMF 150 mcg/160 mcg	20,282	21.49622	1,083,197	1,083,197 vs. S/F 50 mcg/ 250 mcg

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate; vs. = versus.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a] Reference product is the least costly alternative.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case to investigate the impact of an alternative ICS/LABA comparator dose, an alternative proportion of patients admitted to hospital for treatment of a severe exacerbation, and the application of sponsor-provided utility values for the first year of treatment (Table 13).

In the CADTH scenario analyses, the proportion of patients admitted to hospital had a minimal effect on cost-effectiveness estimates, with QMF 150 mcg/160 mcg associated with an ICER of $1,106,692 versus S/F 50 mcg/250 mcg, while QMF 150 mcg/320 mcg was dominated (Table 14). Applying the sponsor-provided utilities for the first year of treatment resulted in an ICER of $255,129 versus S/F 50 mcg/250 mcg; QMF150 mcg/320 mcg remained dominated.

Among patients who require a low-dose ICS/LABA treatment, QMF 150 mcg/160 mcg was associated with an ICER of $2,298,606 versus S/F 50 mcg/100 mcg (Table 14). Among those who require a high-dose ICS/LABA, QMF150 mcg/320 mcg was dominant over S/F 50 mcg/500 mcg.

Given that it is unlikely there would be any health gains with QMF, it should be priced no more than the least expensive comparator. As QMF comes in three separate doses, this would warrant differential pricing among these doses as the price of the least expensive comparator varies by dose. For high-dose QMF, no price reduction would be required as it is less expensive than relevant high-dose ICS/LABA combination therapies. For medium-dose and low-dose versions, there are less expensive ICS/LABA combination therapies and given that QMF is unlikely to provide any incremental benefit, it should be priced no more than the least expensive available option. Single ICS inhalers plus single LABA inhalers are infrequently used and are more expensive than their combination counterparts; hence, this is not relevant in the price comparison.

Issues for Consideration

- Participants in the clinical trials used to provide clinical effectiveness and QoL estimates may not be reflective of the Canadian patient population. The trials upon which the sponsor's submission is based (PALLADIUM and QUARTZ) had no Canadian study sites. Further, for inclusion in these trials, patients were required to have an objective diagnosis of asthma and show reversibility at study entry. In clinical practice, asthma cannot be confirmed in many adults who have an asthma diagnosis (25% to 35%).[11] Were such patients to receive QMF, they would not be expected to show an improvement in asthma symptoms.
- The sponsor's submission asserts that once-daily treatments may lead to improved compliance relative to twice-daily ICS/LABA treatments. Compliance with treatment was not assessed as part of the PALLADIUM or QUARTZ trials and was not considered in the sponsor's economic evaluation. While there is evidence that adherence may be higher with once-daily asthma treatments versus twice-daily asthma treatments, it is not clear whether this translates to improved patient outcomes.[17] The clinical expert consulted by CADTH indicated that adherence may depend, in part, on ease of use of the inhaler device. Breezhaler, the delivery device for QMF, was not considered by the clinical expert to be easy to use relative to other available inhaler devices. Further, as described in the clinical review (Appendix 5), the Breezhaler device is perceived by patients as being more difficult to use compared with other inhalation devices and errors are more common with Breezhaler than with other devices, which may affect patient adherence, clinical effectiveness, and medication costs associated with QMF.

Overall Conclusions

The clinical evidence reviewed by CADTH showed that QMF provided no-to-minimal incremental benefit beyond currently provided treatment options. Therefore, the cost-effectiveness of QMF is largely dictated by its cost relative to other drugs within its treatment class. For patients who require low-dose or medium-dose combinations of ICS/LABA, there

are less expensive treatment options available that would achieve similar health outcomes to QMF. Therefore, for QMF to be considered cost-effective in these patients, the low-dose and medium-dose versions should be priced no more than the least expensive alternative. For patients who require a high-dose ICS/LABA combination, high-dose QMF is less expensive than all alternative comparators and would likely achieve similar health outcomes, making it cost-effective in these patients.

CADTH reanalyses could not address several important limitations. Notably, many ICS/LABA treatments are available in Canada for the maintenance treatment of asthma (Table 8) but owing to a lack of comparative evidence, QMF was compared only to S/F. Other key limitations include uncertainty related to long-term clinical effectiveness and the impact of adverse events. If it is felt that QMF provides equivalent health outcomes for all available treatment options, then these uncertainties will have minimal impact on the cost-effectiveness conclusions.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from the clinical expert consulted by CADTH. Comparators may be recommended (appropriate) practice or actual practice. Costs of comparator products were sourced from the ODB Formulary[7] (accessed July 2020), unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Maintenance Treatment of Moderate to Severe Asthma —Inhaled Corticosteroid/Long-Acting Beta2-Agonist Combination Therapies

Treatment	Strength	Form	Price ($)	Recommended dosage		Daily cost ($)	Annual cost[a] ($)
Indacaterol/mometasone furoate (Atectura Breezhaler)	150 mcg/80 mcg 150 mcg/160 mcg 150 mcg/320 mcg	Inhalation pwd (hard capsules) (30 doses)	58.0800[b]	One capsule for inhalation daily		1.9360	707
Budesonide/formoterol fumarate dihydrate (Symbicort Turbuhaler)	100 mcg/6 mcg 200 mcg/6 mcg	Inhalation pwd (120 doses)	69.5400 90.3600	Low	100 mcg/6 mcg, 2 inhalations twice daily	2.32	846
				Medium	200 mcg/6 mcg, 2 to 4 inhalations daily	1.51 to 3.01	550 to 1,099
				High	200 mcg/6 mcg, > 4 inhalations daily[c]	6.02	2,199
Fluticasone propionate/ salmeterol (Advair)	125 mcg/25 mcg 250 mcg/25 mcg	MDI (120 doses)	105.0700 149.1600	Low	125 mcg/25 mcg, 1 inhalation twice daily	1.75	639
				Medium	125 mcg/25 mcg, 2 inhalations twice daily	3.50	1,278
				High	250 mcg/25 mcg, 2 inhalations twice daily	4.97	1,815
Salmeterol/fluticasone propionate (Advair Diskus, generic)	50 mcg/100 mcg 50 mcg/250 mcg 50 mcg/500 mcg	Inhalation pwd (60 doses)	42.4050 50.7600 72.0600	Low	100 mcg/50 mcg, 1 inhalation twice daily	1.41	516
				Medium	250 mcg/50 mcg, 1 inhalation twice daily	1.69	618
				High	500 mcg/50 mcg, 1 inhalation twice daily	2.40	877
Fluticasone furoate/vilanterol (Breo Ellipta)	100 mcg/25 mcg 200 mcg/25 mcg	Inhalation pwd (30 doses)	86.6300 135.6900	Low	NA	NA	NA
				Medium	100 mcg/25 mcg, 1 inhalation once daily	2.89	1,054

Treatment	Strength	Form	Price ($)	Recommended dosage		Daily cost ($)	Annual cost[a] ($)
				High	200 mcg/25 mcg, 1 inhalation once daily	4.52	1,651
Mometasone furoate/ formoterol fumarate dihydrate (Zenhale)	100 mcg/5 mcg 200 mcg/5 mcg	MDI (120 doses)	97.8600 118.5800	Low	NA	NA	NA
				Medium	100 mcg/5 mcg, 2 inhalations twice daily	3.26	1,191
				High	200 mcg/5 mcg, 2 inhalations twice daily	3.95	1,443

MDI = metered-dose inhaler; NA = not applicable; pwd = powder.

[a] Annual costs are calculated based on 365 days per year.

[b] Sponsor-submitted price.[2]

[c] Based on clinical expert feedback.

Appendix 2: Submission Quality

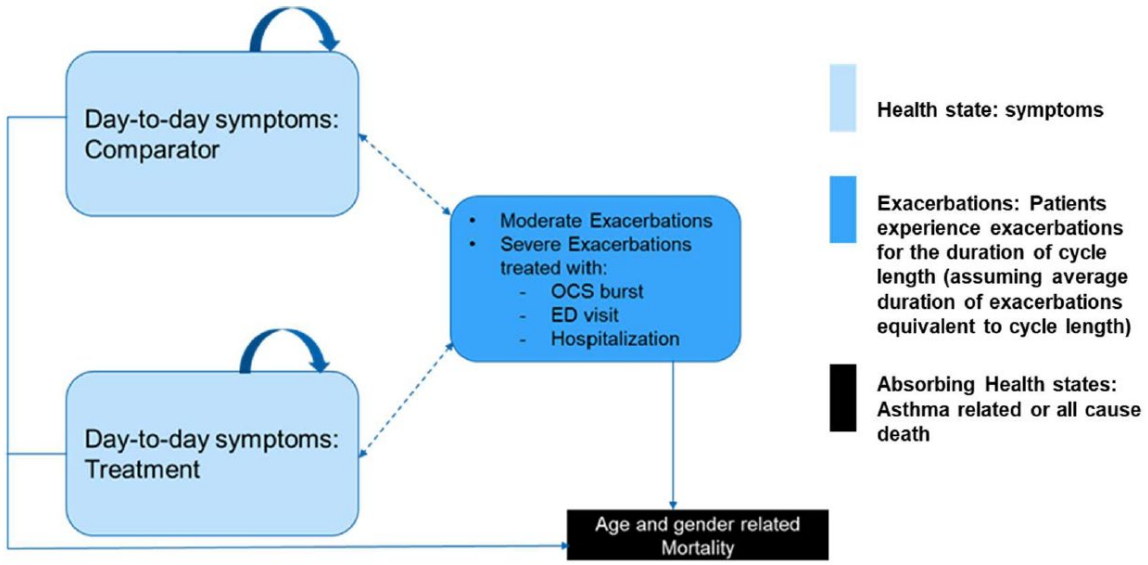
Table 9: Submission Quality

Description	Yes	No	Comments
The population is relevant, with no critical intervention missing and no relevant outcome missing.	☐	☒	The sponsor's analyses considered only one of several currently available ICS/LABA comparator treatments. The participants in the clinical trials may not reflect those seen in clinical practice in Canada. The sponsor's model addressed the cost-effectiveness in adults, with a cohort starting age of 46 years to 48 years; no subgroup analyses for adolescents were provided.
The model has been adequately programmed and has sufficient face validity.	☒	☐	
The model structure is adequate for the decision problem.	☒	☐	The sponsor's analysis does not account for adverse events. Adverse events were identified as being of concern to patients and may be associated with additional costs to the health care system. The risk of adverse events may be higher at high ICS doses.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	☒	☐	The range for utility values was constructed as ± 5% of the mean estimate and does not reflect the full range of possible values. Moderate exacerbation rates were inappropriately calculated by subtracting the rate of severe exacerbations from the rate of all exacerbations. This discrepancy affected all treatments and would not be expected to substantially affect costs or QALY estimates.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	☒	☐	
The submission was well organized and complete, and the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	☒	☐	

ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist; QALY = quality-adjusted life-year.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



ED = emergency department; OCS = oral corticosteroid.

Source: Sponsor's Pharmacoeconomic Submission.[10]

Detailed Results of the Sponsor's Base Case

The following section provides additional information about the two base-case analyses submitted by the sponsor. The analyses were based on the findings from the PALLADIUM and QUARTZ trials.

Table 10: Disaggregated Summary of Sponsor's Results in PALLADIUM Study

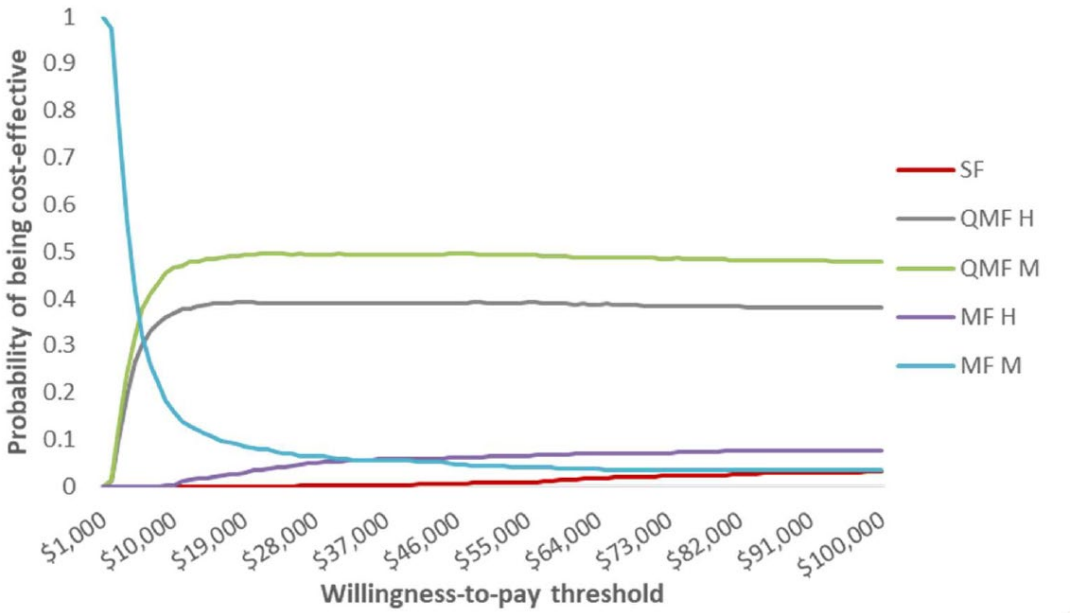
Drug	QMF 150 mcg/ 320 mcg	QMF 150 mcg/ 160 mcg	S/F 50 mcg/ 500 mcg	MF 800 mcg	MF 400 mcg
Discounted LYs					
Total	27.04	27.04	27.04	27.04	27.04
Discounted exacerbations, number per patient					
Total (all exacerbations)	13.24	12.99	14.04	20.05	28.36
Moderate exacerbations	9.73	9.44	10.27	15.12	20.54
Severe exacerbations					
Requiring hospitalization	0.18	0.18	0.19	0.24	0.39
Requiring ED visit	0.17	0.18	0.19	0.24	0.39
Requiring OCS burst	3.16	3.20	3.39	4.43	7.04
Discounted costs ($)					
Total	20,281.61	20,284.24	36,836.24	27,184.47	15,378.58

Drug	QMF 150 mcg/ 320 mcg	QMF 150 mcg/ 160 mcg	S/F 50 mcg/ 500 mcg	MF 800 mcg	MF 400 mcg
Drug costs	19,121.95	19,121.95	35,586.98	25,569.68	12,784.84
Exacerbation costs	1,159.66	1,162.28	1,249.26	1,614.78	2,593.74

ED = emergency department; LY = life-year; MF = mometasone furoate; OCS = oral corticosteroid; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate.

Source: Sponsor's Pharmacoeconomic Submission.[10]

Figure 2: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis in the PALLADIUM Study



MF H = mometasone furoate high dose (800 mcg); MF M = mometasone furoate medium dose (400 mcg); QMF H = indacaterol/mometasone furoate high dose (150 mcg/320 mcg); QMF M = indacaterol/mometasone furoate medium dose (150 mcg/160 mcg); S/F = salmeterol/fluticasone propionate.

Source: Sponsor's Pharmacoeconomic Submission.[10]

Table 11: Disaggregated Summary of Sponsor's Economic Evaluation Results in the QUARTZ Study

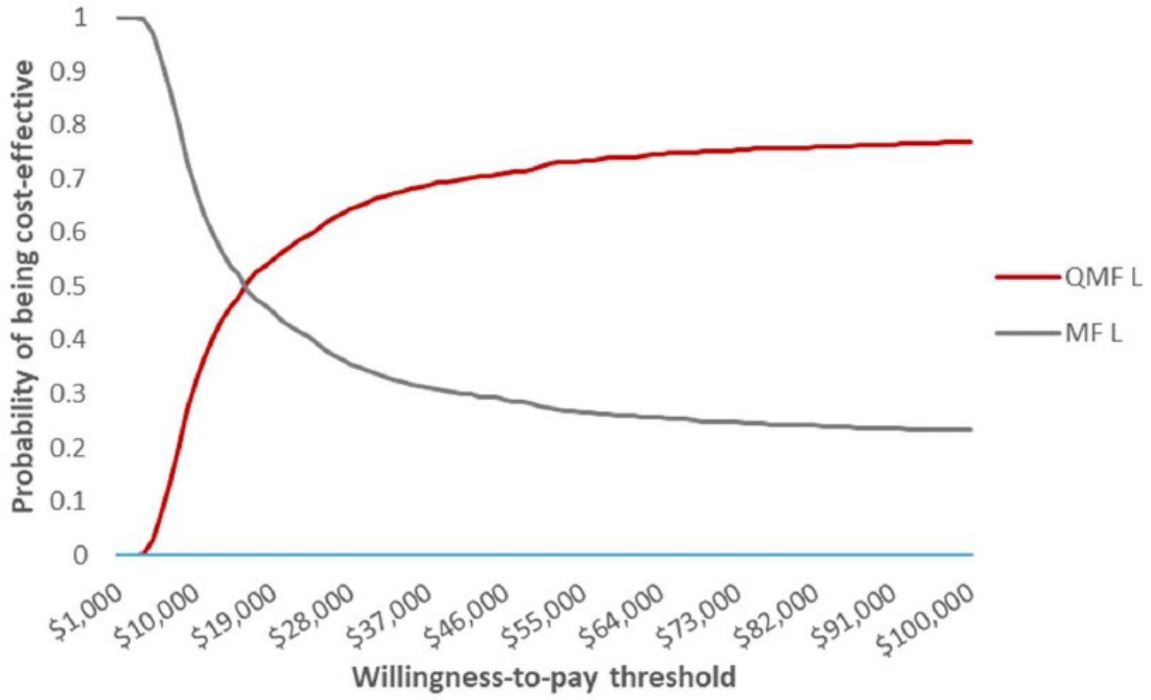
Drug	QMF 150 mcg/80 mcg	MF 200 mcg
Discounted LYs		
Total	28.29	28.29
Discounted exacerbations, number per patient		
Total (all exacerbations)	5.67	18.90
Moderate exacerbations	3.39	10.18
Severe exacerbations		
Requiring hospitalization	0.12	0.44
Requiring ED visit	0.11	0.44

Drug	QMF 150 mcg/80 mcg	MF 200 mcg
Requiring OCS burst	2.05	7.85
Discounted costs ($)		
Total	20,773.14	9,581.08
Drug costs	20,005.18	6,688.72
Exacerbation costs	767.96	2,892.36

ED = emergency department; LY = life-year; MF = mometasone furoate; OCS = oral corticosteroid; QMF = indacaterol/mometasone furoate.

Source: Sponsor's Pharmacoeconomic Submission.[10]

Figure 3: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis in the QUARTZ Study



MF L = mometasone furoate low dose (200 mcg); QMF L = indacaterol/mometasone furoate low dose (150 mcg/80 mcg).

Source: Sponsor's Pharmacoeconomic Submission.[10]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 12: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Sponsor's base case (corrected)	MF 400 mcg	15,379	20.86	—
	QMF 150 mcg/320 mcg	20,274	21.63	Extendedly dominated
	QMF 150 mcg/160 mcg	20,282	21.72	5,719
	S/F 50 mcg/500 mcg	24,978	21.50	Dominated
	MF 800 mcg	27,171	21.19	Dominated
CADTH reanalysis 1: S/F moderate dose	S/F 50 mcg/250 mcg	17,961	21.49409	—
	QMF 150 mcg/160 mcg	20,286	21.67344	12,964
	QMF 150 mcg/320 mcg	20,290	21.65067	Dominated
CADTH reanalysis 2: No difference in utilities between treatments	QMF 150 mcg/160 mcg	20,284	21.50093	—
	QMF 150 mcg/320 mcg	20,285	21.50077	Dominated
	S/F 50 mcg/250 mcg	24,980	21.49862	Dominated
CADTH base case	S/F 50 mcg/250 mcg	17,964	21.49408	—
	QMF 150 mcg /320 mcg	20,281	21.49617	Extendedly dominated
	QMF 150 mcg/160 mcg	20,282	21.49622	1,083,197

ICER = incremental cost-effectiveness ratio; MF = mometasone furoate; QALY = quality-adjusted life year; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate.

Note: The submitted analysis is based on publicly available prices of the comparator treatments.

Scenario Analyses

Table 13: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario analyses		
1. Proportion of severe exacerbations that require hospitalization	5%	1%
2. Utility values	No difference in utilities between treatments	Sponsor-provided utility values applied for the first year of treatment
3. ICS/LABA dose	Medium-dose ICS/LABA (S/F 50 mcg/250 mcg)	Low-dose ICS/LABA (S/F 50 mcg/125 mcg vs. QMF 150 mcg/80 mcg)
4. ICS/LABA dose	Medium-dose ICS/LABA (S/F 50 mcg/250 mcg)	High-dose ICS/LABA (S/F 50 mcg/500 mcg vs. QMF 150 mcg/320 mcg)

ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate; vs. = versus.

Table 14: CADTH Scenario Analyses Results

Drug	Total costs ($)	Total QALYs	ICER vs. reference ($/QALY)	Sequential ICER ($/QALY)
Hospitalization rate				
S/F 50 mcg/250 mcg[a]	17,272	21.49352	–	–
QMF 150 mcg/160 mcg	19,640	21.49566	1,106,692	1,106,692
QMF 150 mcg/320 mcg	19,642	21.49548	1,204,616	Dominated
1-year utility benefit[b]				
S/F 50 mcg/250 mcg[a]	17,965	21.49429	–	–
QMF 150 mcg/160 mcg	20,285	21.50339	255,129	255,129
QMF 150 mcg/320 mcg	20,285	21.50141	325,995	Dominated
Alternative comparator (low-dose ICS/LABA)				
S/F 50 mcg/125 mcg[a]	15,214	21.49322	–	–
QMF 150 mcg/80 mcg	20,283	21.49542	2,298,606	2,298,606
Alternative comparator (high-dose ICS/LABA)				
QMF 150 mcg/320 mcg[a]	20,285	21.49453	–	–
S/F 50 mcg/500 mcg	24,974	21.49232	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; QALY = quality-adjusted life-year; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] Reference product is least costly alternative.

[b] Deterministic analysis.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - Assumptions regarding the distribution of claims for asthma relative to other conditions (e.g., chronic obstructive pulmonary disease [COPD]) could not be verified, and the proportion of claims attributed to asthma were considered underestimated by the clinical expert consulted by CADTH. Claims were further divided into three market segments (low-dose, medium-dose, and high-dose) for ICS/LABA treatments, and assumptions were required regarding the distribution of claims between segments for some comparator treatments. CADTH was unable to verify the validity of these assumptions.
  - The sponsor's submission did not differentiate between incident and prevalent use of ICS/LABA treatments. The uptake of QMF may differ between incident and prevalent users, and the clinical expert consulted by CADTH indicated that it was unreasonable to expect equal market uptake between groups. Prevalent users of an ICS/LABA treatment (i.e., those taking an ICS/LABA but whose asthma remains uncontrolled) at a low dose or moderate dose would be more likely to increase the ICS dose within the current ICS/LABA formulation rather than switch to a different ICS/LABA formulation. New users of ICS/LABA treatments (i.e., those initiating an ICS/LABA treatment after failing to achieve control with an ICS alone) may be more likely than prevalent users to initiate QMF.
  - Uptake of QMF was assumed to be 3.5% in the first year, 8.6% in the second year, and 10.7% in the third year. The clinical expert consulted by CADTH indicated that this is likely an overestimate, owing to the number of currently available ICS/LABA treatments.
- Owing to the high degree of uncertainty around these model parameters, CADTH did not reanalyze the sponsor's budget impact analysis (BIA) submission. The reimbursement of QMF will likely not add significant costs to the health care system, but whether QMF is cost-saving as suggested by the sponsor is uncertain.

Summary of Sponsor's Budget Impact Analysis

The submitted BIA[18] assessed the introduction of three strengths of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. The BIA was undertaken from the perspective of the Canadian publicly funded health care payer over a three-year time horizon (2021 to 2023) using a claims-based approach, and the sponsor's submission considered only drug costs. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Government of Canada's Non-Insured Health Benefits program.

The sponsor estimated the number of eligible patients by use of historical drug utilization data from 2016 to 2020. Two scenarios were considered: (1) a reference scenario in which QMF was not reimbursed, and (2) a new drug scenario in which QMF was reimbursed. Comparators in the BIA were Health Canada–approved ICS/LABA combination inhalers (i.e., budesonide/formoterol fumarate dihydrate [Symbicort Turbuhaler], S/F [Advair, Advair Diskus], MF/formoterol fumarate dihydrate [Zenhale], and fluticasone furoate/vilanterol [Breo Ellipta]). The treatments were divided into low-dose, medium-dose, and high-dose market segments on the basis of recommended daily doses from a previous CADTH pharmacoeconomic review.

Drug prices were based on provincial formularies. For drugs indicated in the treatment of COPD, data from IQVIA Rx Dynamics were applied to estimate the percentage used for each indication by drug and strength. For drugs or strength labelled only for asthma, all units were considered to be used in asthma. For drugs where the same dosage can be used in

two different market segments depending on the number of inhalations per day (i.e., Advair 125 mcg/25 mcg, Symbicort 200 mcg/6 mcg), the number of claims was split between market segments based on the distribution of claims for Advair Diskus (100 mcg/50 mcg and 250 mcg/50 mcg) and Breo Ellipta (100 mcg/25 mcg and 200 mcg/25 mcg). For all comparators, units were transformed into the number of patients by dividing the number of units by the number of units per year based on the dosing schedule.

The market uptake for QMF was assumed to be equivalent at all dose levels (3.5% in year 1, 8.6% in year 2, and 10.7% in year 3). Market share for the comparators varied by jurisdiction and the sponsor assumed that QMF would have the same impact on all current available treatment (equal displacement).

The sponsor conducted deterministic one-way scenario analyses to assess the impact of assuming all claims were for the treatment of asthma and assuming 10% higher or lower uptake of QMF at each dose level.

Key inputs to the BIA are documented in Table 15.

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Number of eligible patients per year[a] (year 1/year 2/year 3)	
Low dose	[redacted]
Moderate dose	[redacted]
High dose	[redacted]
Market uptake (3 years)	
Uptake (reference scenario)	
QMF (150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg)	0%, 0%, 0%
Comparators	Jurisdiction specific[b]
Uptake (new drug scenario)	
QMF (150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg)	3.5%, 8.6%, 10.7%
Comparators	Jurisdiction specific[c]
Cost of treatment (per patient)	
Cost of annual treatment[d]	
QMF (150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg)	$707
Comparators	Jurisdiction specific

QMF = indacaterol/mometasone furoate.

[a] Pan-Canadian estimates were not provided. CADTH summed the sponsor's estimated number of eligible patients across jurisdictions. The sponsor's estimated number of patients in each jurisdiction was based on the number of forecasted units per year, divided by the number of units per year per patient.

[b] The projected market uptake for each ICS/LABA comparator in the reference scenario was based on jurisdiction-specific historic claims data.

[c] QMF was assumed to have the same impact on all currently available treatment (same displacement).

Summary of the Sponsor's Budget Impact Analysis Results

The sponsor's base-case analysis found that the reimbursement of QMF as a maintenance treatment for asthma will be cost-saving (expected savings: $3,259,832 in year 1, $8,346,710 in year 2, and $10,804,145 in year 3). Reimbursing QMF was estimated by the sponsor to save $22,410,687 over the three-year period

In each of the sponsor's scenario analyses, QMF was cost-saving, with savings ranging from $20,169,618 to $25,109,164 over three years.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that may have notable implications on the results of the BIA. There is considerable uncertainty associated with the sponsor's estimates, described as follows:

- **Uncertainty about the indication for prescription claims.** The sponsor adopted a claims-based approach to estimate the number of patients eligible for treatment. Because claims do not provide information about the indication, for some comparators, it is unclear what proportion of claims were for asthma treatment. Multiple comparators are indicated for both asthma and COPD (i.e., Advair Diskus, Symbicort, Breo Ellipta). The sponsor estimated the percentage of claims for asthma (versus COPD) by use of IQVIA Rx Dynamics; however, CADTH was unable to verify these estimates. The clinical expert consulted by CADTH indicated that the sponsor's estimates of the percentage of units used in the treatment of asthma was likely underestimated. Further, for drugs or strengths that are labelled or reimbursed only for asthma, all units were assumed to be used in the treatment of asthma (i.e., off-label use was not addressed).
  - The sponsor provided a scenario analysis in which all units were assumed to be used in asthma. This resulted in 20% higher total sales for QMF ($29,213,155 over three years) and an additional 12% cost savings relative to the base case (–$25,109,164).
- **Uncertainty about the market share of comparator treatments.** The sponsor's submission was divided into three market segments (low-dose, medium-dose, high-dose) on the basis of a recommended dosing schedule for ICS/LABA treatments from a previous CADTH pharmacoeconomic review.[19] For some comparator treatments, the same dose can be used in two market segments, depending on the number of inhalations per day (i.e., Advair 125 mcg/25 mcg, Symbicort 200 mcg/6 mcg). For these comparators, the sponsor assumed that the distinction between market segments would be similar to that for other comparators. For example, to segment Advair 125 mcg/25 mcg into low-dose and medium-dose segments, the sponsor assumed that the split would be equivalent to that for Advair Diskus 100 mcg/50 mcg and 250 mcg/50 mcg. For Advair Diskus, the split between claims for the low-dose, medium-dose, and high-dose formulations was [redacted], [redacted] and [redacted] respectively. The sponsor then assumed that the split between Advair Diskus 100 mcg and 250 mcg ([redacted] versus [redacted]) would apply to Advair 125 mcg/25 mcg ([redacted] of claims would be for the low-dose market share, [redacted] for the medium-dose market share). This split varied by jurisdiction. CADTH was unable to verify whether these assumptions are reasonable.
  - Given that QMF will provide cost savings for those who require a high dose but could increases costs for those who require a medium dose or low dose, having an accurate breakdown of what dose QMF would be used for will have a large influence on budget impact.
- **Uncertainty about the uptake of QMF among incident versus prevalent ICS/LABA users.** The sponsor's BIA did not distinguish between patients who were initiating an ICS/LABA for the first time (incident use) and those who were uncontrolled on current ICS/LABA treatment (prevalent use). The clinical expert consulted by CADTH indicated that there would likely be differential uptake of QMF between incident and prevalent users. Among those initiating an ICS/LABA for the first time, the clinical expert indicated that patients are typically started on a medium-dose or high-dose ICS/LABA, with very few started at low dose. Among prevalent users, it is more likely that the ICS dose would be increased to the highest dose (within an ICS/LABA) than switched to a different ICS/LABA treatment.

- If it is felt that prevalent users of ICS/LABAs would not switch to a new formulation, then this would reduce the budget impact.

- **Uncertainty regarding the uptake of QMF and displacement of existing ICS/LABA treatments.** The market uptake of QMF was assumed to be 3.5% in year 1, 8.6% in year 2, and 10.7% in year 3, based on the sponsor's internal assumptions. The clinical expert consulted by CADTH indicated that because multiple ICS/LABA treatments are available and because uptake is more likely among incident ICS/LABA users, an assumption of capturing 10% of the market share was unreasonable. Further, the sponsor assumed that the uptake of QMF would be consistent across low-dose, medium-dose, and high-dose QMF. The clinical expert indicated that few patients who require an ICS/LABA would be prescribed a low-dose formulation, and that a patient uncontrolled on a low-dose or medium-dose ICS/LABA would be more likely to transition to a high-dose ICS/LABA than to switch to an alternative ICS/LABA treatment. The clinical expert consulted by CADTH indicated that the projected uptake of QMF is uncertain but likely overestimated. The validity of the assumption of equal displacement of currently available treatments is similarly uncertain, given the availability of multiple ICS/LABA treatments.
  - There are cheaper ICS/LABA alternatives for low-dose and medium-dose patients. If QMF were to replace these comparators, then budget impact would increase. If it was to replace more expensive alternatives, then QMF may generate cost savings.
- **Inappropriate comparator drug costs.** While the sponsor's submission states that the generic cost was incorporated into the BIA in provinces where a generic version is available, CADTH identified several discrepancies between the sponsor's submission and provincial drug formularies. For example, in British Columbia, the price of Advair Diskus 500 mcg/50 mcg was included in the sponsor's model as $2.0417 per unit, while the amount covered by BC PharmaCare is $1.2971 per unit. This discrepancy may, at least in part, be owing to changing drug prices on the provincial formularies over time. Further, the sponsor assumed that high-dose Symbicort Turbuhaler (200 mcg/6 mcg) would be administered as four inhalations twice daily. The clinical expert consulted by CADTH indicated that few patients would be prescribed this dose and that this regimen would be used only to provide rapid symptom relief. High-dose Symbicort would typically be prescribed as two inhalations twice daily.

  The cost of some comparators was thus overestimated, leading to a potential overestimation of the savings with reimbursement of QMF.

  Any BIA reanalysis would need to incorporate the most up-to-date costs.
- Additional limitations were identified, but were not considered to be key limitations. These include discrepancies between the BIA report and submitted Excel model. For example, the number of treated patients described in the sponsor's report (sponsor's Table 4: "Number of treated patients [reference scenario]") corresponds to the model values for Ontario; however, the sponsor's table is not labelled as such. Further, the sponsor's model does not provide the total number of patients eligible for treatment from a pan-Canadian perspective.

CADTH Reanalyses of the BIA

CADTH did not undertake reanalysis of the sponsor's BIA. QMF at the submitted price is less expensive than some ICS/LABA comparators, depending on the ICS/LABA dose (Table 8). Owing to limitations described above, it is uncertain if QMF will be cost-saving. Although QMF will likely not introduce significant costs to the health care system, whether it will be cost-saving to drug plans will depend on how many patients switch to QMF and from what comparator.

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