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CADTH COMMON DRUG REVIEW

# Pharmacoeconomic Review Report

## FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL (TRELEGY ELLIPTA)

(GlaxoSmithKline plc.)

Indication: Chronic obstructive pulmonary disease (COPD) not adequately treated by a combination of inhaled corticosteroid (ICS) and long-acting beta-2-agonist (LABA)


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# Abbreviations

| | |
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| **BUD** | budesonide |
| **CDR** | Common Drug Review |
| **CI** | confidence interval |
| **COPD** | chronic obstructive pulmonary disease |
| **CUA** | cost-utility analysis |
| **EQ-5D** | EuroQuol 5-Dimensions questionnaire |
| **$FEV_1$** | forced expiration volume in one second |
| **FF** | fluticasone furoate |
| **FOR** | formoterol fumarate |
| **FP** | fluticasone propionate |
| **FP/SAL** | fluticasone propionate/salmeterol |
| **ICS** | inhaled corticosteroid |
| **ICUR** | incremental cost-utility ratio |
| **LABA** | long-acting beta-2-agonists |
| **LAMA** | long-acting muscarinic antagonist |
| **MITT** | multiple inhaler triple therapy |
| **NMA** | network meta-analysis |
| **QALY** | quality-adjusted life-year |
| **SAL** | salmeterol |
| **SITT** | single inhaler triple therapy |
| **SGRQ-C** | St. George's Respiratory Questionnaire for COPD patients |
| **TIO** | tiotropium |
| **UMEC** | umeclidinium |
| **VI** | vilanterol |
| **6MWD** | six-minute walking distance |

## Table 1: Summary of the Manufacturer's Economic Submission

| | |
|---|---|
| **Drug Product** | Fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (FF/UMEC/VI;100/62.5/25 mcg) |
| **Study Question** | Is FF/UMEC/VI (a single inhaler triple therapy, SITT) a cost-effective alternative to FF/VI and UMEC/VI (dual-therapy regimens) and to tiotropium (TIO) plus FP/SAL (a multiple inhaler triple therapy, MITT) in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and risk of exacerbation despite current maintenance therapy with a LAMA, LAMA/LABA or ICS/LABA, or those who are currently treated with an ICS/LAMA/LABA regimen? |
| **Type of Economic Evaluation** | Cost-utility analysis |
| **Target Population** | Patients with moderate to severe COPD and risk of exacerbation despite current maintenance therapy with a LAMA, LAMA/LABA or an ICS/LABA, or those who are currently treated with MITT |
| **Treatment** | FF/UMEC/VI once a day |
| **Outcomes** | • Moderate and severe exacerbations<br>• Life-years<br>• Quality-adjusted life-years (QALYs) |
| **Comparators** | Dual therapies:<br>• FF/VI (100/25 mcg) once daily<br>• UMEC/VI (62.5/25 mcg) once daily<br><br>MITT regimens:<br>• TIO 18 mcg + FP/SAL (250/50 mcg) twice daily<br>• TIO 18 mcg + FP/SAL (500/50 mcg) twice daily |
| **Perspective** | Canadian health care perspective |
| **Time Horizon** | Lifetime horizon (i.e., 25 years, with a starting age of 65.3 years) |
| **Results for Base Case** | Compared with dual therapies:<br>• FF/VI: FF/UMEC/VI provided an additional 0.1322 QALYs, at an additional cost of $2,598 per patient, for an ICUR of $19,649 per QALY.<br>• UMEC/VI: FF/UMEC/VI provided an additional 0.1211 QALYs, at an additional cost of $1,801 per patient, for an ICUR was $14,864.<br>Compared with triple therapies:<br>• FF/UMEC/VI dominates MITT regimens; i.e., FF/UMEC/VI is associated with lower total costs, while clinical benefits were comparable to those estimated for MITT. |
| **Key Limitations** | • The predictive accuracy of the epidemiology model in estimating long-term outcomes is questionable, in particular with regards to exacerbations and health-related quality of life. This adds uncertainty to the results of the analysis.<br>• The epidemiological study and resource use information was based on international sources, and no attempt was made to isolate data for Canadian centres or validate the information for the Canadian setting.<br>• Utility values were based on an inaccurate mapping algorithm, instead of directly observed utility values in the pivotal IMPACT trial, which likely favours FF/UMEC/VI over comparators.<br>• A limited set of comparators were included, where relevant comparators such as BUD/FOR were omitted from the analysis.<br>• The NMA [redacted].<br>• The patent for FP/SAL has expired; as such, generic entrants may reduce the price of FP/SAL in the near future. |

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| **CDR Estimates** | • A number of important limitations could not be explored in the CDR reanalyses, including the choice of utility and resource use values, relative treatment effect for dual therapies not based on network meta-analysis, predictive accuracy of the epidemiological model, and comparison with other relevant drug therapies that were not part of the submission.<br>• In the CADTH base case, the cost of generic FP/SAL was assumed to be the same as BUD/FOR and the cost of a physician home visit was increased to be the same as a clinic visit.<br>• The results showed that the ICUR for FF/UMEC/VI was $21,189 per QALY when compared with FF/VI and $17,022 per QALY when compared with UMEC/VI.<br>• For comparison with TIO+FP/SAL 250/50 mcg, the ICUR for FF/UMEC/VI was $137,990 but FF/UMEC/VI was dominant (less total costs and greater QALYs) when compared with TIO+FP/SAL 500/50 mcg. However, ICURs for the comparison with TIO+FP/SAL were unstable and associated with substantial decision uncertainty.<br>• CDR scenario analyses showed:<br>o when compared with FF/VI and UMEC/VI, ICUR for FF/UMEC/VI remained under $50,000 per QALY when the cost of FP/SAL was reduced to 25% of the brand price and/or ER visit cost was increased.<br>o when compared with TIO+FP/SAL, the ICUR for FF/UMEC/VI was $82,562 when the price of FF/UMEC/VI was reduced by 5% (i.e., FF/UMEC/VI was dominant in 13.6% and dominated in 17.9% simulations).<br>• When the price of FF/UMEC/VI was reduced by 15%, FF/UMEC/VI became the dominant treatment (i.e., FF/UMEC/VI was dominant in 25.8% and dominated in 11.7% simulations).<br>• However, when the price of FP/SAL was reduced to 25% of the brand price, TIO+FP/SAL became more likely to be the cost-effective option (i.e., TIO+FP/SAL was dominant in 37.5% and dominated in 0.3% simulations).<br>• This implies that if the generic price of FP/SAL is 25% of the branded FP/SAL, a greater price reduction for FF/UMEC/VI is required to achieve an ICUR of below $50,000 for FF/UMEC/IV. |

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| **Drug** | Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) |
| **Indication** | For long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA |
| **Reimbursement Request** | FF/UMEC/VI should be recommended where the following clinical criteria are met:<br>• moderate to severe COPD, as defined by spirometry; and<br>• at risk of exacerbations despite a long-acting bronchodilator (LAMA or LABA); or<br>o symptomatic or at risk of exacerbations despite a LAMA/LABA or ICS/LABA; or<br>o currently on a LAMA/ICS/LABA. |
| **Dosage Form** | Inhalation |
| **NOC Date** | April 4, 2018 |
| **Manufacturer** | GlaxoSmithKline plc |

# Executive Summary

## Background

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 mcg is a combination of an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta-2-agonist (LABA).[1] It is available as a single inhaler triple therapy and approved for the long-term, once daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA. The submitted price is $132.20 for 30 doses, for a daily per patient cost of $4.41 or $1,608 annually.[2]

The manufacturer conducted a cost-utility analysis (CUA) to assess FF/UMEC/VI compared with dual therapies (e.g., FF/VI [ICS/LABA], UMEC/VI [LABA/LAMA]) and multiple inhaler triple therapy (MITT – tiotropium + fluticasone propionate/salmeterol; TIO + FP/SAL) in patients with moderate to severe COPD who were not adequately treated by a combination of ICS and LABA.[2] The CUA used a previously published decision model (GALAXY), which predicted outcomes and costs in COPD patients over their lifetimes (25 years).[3] The GALAXY model was primarily based on two data sources: a three-year global epidemiology study (ECLIPSE) used to predict COPD disease progression and quality of life[4]; and a three-year international randomized controlled trial (TORCH) used to estimate health services resource use in COPD patients.[5] The ECLIPSE study used linked statistical equations to predict lung function, exacerbations, exercise capacity, and symptoms over time — these attributes, along with patient baseline variables, were then used to predict quality of life outcomes (measured in terms of St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)) and health services resource use. Predicted SGRQ-C was then mapped to the preference-based EuroQuol 5-Dimensions questionnaire (EQ-5D) to estimate quality-adjusted life-years (QALYs), using a published mapping algorithm.[6] Predicted resource use was used to calculate costs from the perspective of the Canadian public health care payer, using country-specific unit costs.

Treatment effects were applied to the GALAXY model in terms of change in $FEV_1$ from baseline, reduction in moderate and severe exacerbations, and change in SGRQ-C from

baseline. Treatment effects of FF/UMEC/VI versus the two dual therapies — i.e., FF/VI and UMEC/VI — were based on a large (n = 10,355) randomized controlled trial (IMPACT) conducted by the manufacturer.[7] The treatment effect of FF/UMEC/VI versus TIO + FP/SAL was based on evidence synthesis considering direct and indirect comparisons (i.e., a network meta-analysis, or NMA).[8] Finally, exacerbation reduction and change in SGRQ-C predicted by the GALAXY model using the above mentioned treatment effects was compared to that observed in the IMPACT trial and NMA, and subsequently adjusted to account for the difference in treatment effect.

The manufacturer analysis found that FF/UMEC/VI had an incremental cost per QALY of $19,649 compared with FF/VI, and $14,864 per QALY compared with UMEC/VI. When compared with TIO + FP/SAL 250/50 mcg, FF/UMEC/VI was dominant — but had a 29.7% chance of being dominant (i.e., lower cost and higher QALYs) and 10% chance of being dominated (i.e., higher cost and lower QALYs). Finally, when compared with TIO + FP/SAL 500/50 mcg, FF/UMEC/VI was dominant — but had a 63.2% chance of being dominant and a 0.3% chance of being dominated.

## Summary of Identified Limitations and Key Results

A number of key limitations were identified with the manufacturer's pharmacoeconomic analyses.

The decision model used for CUA proved to be less accurate in predicting clinical outcomes, in particular a reduction in exacerbations (i.e., under-predicting the treatment effect of FF/VI and UMEC/VI and over-predicting the effect of MITT).[2] Subsequent predictions of quality of life in terms of SGRQ-C, based on predicted clinical outcomes and treatment effects, were also found to be less accurate. Predictions were adjusted to be closer to the IMPACT trial and the NMA using a post-hoc adjustment. This issue with predictive accuracy increases uncertainty, which is not reflected in the results. Furthermore, the use of this type of model limits the possibility to test other sets of values (e.g., health utilities) to understand the full impact of variables.

Utility-based quality of life data were collected in the IMPACT trial using the EQ-5D questionnaire. However, these data were not used in the economic analysis because of the inflexibility of the model in terms of the data requirements. Instead, a published mapping algorithm based on SGRQ-C was used.[6] The authors of the mapping study suggested caution in its use for health technology assessment because of prediction inaccuracies of the algorithm.[6] Importantly, the IMPACT trial found that [redacted].

Resource use was based on a multi-centre study with 16 of the 444 centres in Canada.[5] No attempt was made to isolate information from Canadian centres or to verify that the practice patterns observed in this study are similar to that in Canada.

Relative treatment effects for dual therapies were based on the IMPACT trial, while treatment effect compared with MITT was based on the NMA. Since the NMA makes use of all available evidence, the treatment effects of FF/UMEC/VI versus FF/VI and UMEC/VI should also be derived from the NMA and not a single study.

The NMA had some limitations. [redacted]

To address the decision problem, all relevant comparators should have been included in the economic analysis and results presented sequentially to determine the most cost-effective treatment. However, a limited set of comparators were used in the study and the choice of comparators in the economic evaluation was not clearly justified. For instance, budesonide/formoterol fumarate (BUD/FOR) and beclomethasone dipropionate, FOR and glycopyrronium combinations used in the recent trials were not included as comparators. As such, the cost-effectiveness of some routinely used drug combinations, depending on the use of treatments within participating jurisdictions, is unknown.

In the CADTH base case (accounting for the potential generic availability of FP/SAL by setting the price equal to BUD/FOR and using an appropriate cost of physician home visits), the incremental cost-utility ratio (ICUR) for FF/UMEC/VI was $21,189 per QALY compared with FF/VI and $17,022 per QALY when compared with UMEC/VI. For comparison with TIO + FP/SAL 250/50 mcg, the ICUR for FF/UMEC/VI was $137,990 but FF/UMEC/VI was dominant (lower total costs, greater QALYs) when compared with TIO + FP/SAL 500/50 mcg. All ICURs for TIO + FP/SAL comparisons were unstable and associated with substantial uncertainty.

Furthermore, the CADTH Common Drug Review scenario analyses (where the cost of FP/SAL was reduced to 25% of the brand price and emergency room costs increased to reflect practice) showed that, when compared to dual therapy (FF/VI and UMEC/VI), the ICUR for FF/UMEC/VI remained under $50,000 per QALY in all scenarios. Compared with TIO + FP/SAL (250/50 mcg), when the price of FF/UMEC/VI was reduced by 5%, the ICUR for FF/UMEC/VI was $82,562 per QALY (FF/UMEC/VI was dominant in 13.6% and dominated in 17.9% simulations). When the price of FF/UMEC/VI was reduced by 15%, FF/UMEC/VI became the dominant treatment (FF/UMEC/VI was dominant in 25.8% and dominated in 11.7% simulations). However, when the price of FP/SAL was reduced to 25% of the brand price to reflect generic entrants, while maintaining the submitted price of FF/UMEC/VI, TIO + FP/SAL became more likely to be the cost-effective option (i.e., TIO + FP/SAL was dominant in 37.5% and dominated in 0.3% simulations). This implies that if FP/SAL is assumed to cost substantially lower, a greater price reduction for FF/UMEC/VI is required to achieve an ICUR of below $50,000 for FF/UMEC/IV. However, the ICUR for FF/UMEC/VI compared with TIO + FP/SAL remained unstable, resulting in uncertainty in ICUR estimates.

## Conclusions

Based on CADTH reanalyses to reflect the potential generic price of FP/SAL and the higher cost of physician home visits, the ICUR for FF/UMEC/VI compared with FF/VI and UMEC/VI is likely to be higher than suggested by the manufacturer, although it appears to remain under $50,000 per QALY. When compared with TIO + FP/SAL, the results were unstable and, as such, associated with large decision uncertainty, and were highly sensitive to price changes in FF/UMEC/VI, as well as FP/SAL.

The CADTH reanalyses could not address a number of potentially significant limitations of the submission, including the limitations of statistical analysis of the epidemiological study, the predictive inaccuracy of the decision model, the imprecision of the utility mapping algorithm, the non-inclusion of other relevant comparators, and limiting the treatment effect estimation to a single trial. Therefore, results of the economic analysis should be considered with caution.

# Information on the Pharmacoeconomic Submission

## Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer performed a cost-utility analysis comparing FF/UMEC/VI (ICS/LAMA/LABA), a single inhaler triple therapy (SITT), to two dual therapy regimens — i.e., FF/VI (ICS/LABA, Breo Ellipta) and UMEC/VI (LABA/LAMA, Anoro Ellipta) — and to a multiple inhaler triple therapy (MITT) regimen — i.e., TIO + FP/SAL (LAMA + ICS/ LABA, Spiriva + Advair).[2] The intended target population are patients with chronic obstructive pulmonary disease (COPD) who remain symptomatic and at risk of an exacerbation despite current maintenance therapy with a LAMA, LAMA/LABA, or an ICS/LABA, or those who are currently treated with an ICS/LAMA/LABA regimen. The economic analysis included forced expiration volume in one second ($FEV_1$) and the number of moderate and severe exacerbations as disease progression outcomes, and the quality-adjusted life-years (QALYs) as the final outcome.[2] Relative efficacy estimates of FF/UMEC/VI versus FF/VI (ICS/LABA) and FF/UMEC/VI versus UMEC/VI (LAMA/LABA) were based on the IMPACT trial (n = 10,355) conducted in 37 countries, including Canada, with a one-year follow-up period.[7] Relative efficacy of TIO + FP/SAL (ICS/LAMA/LABA) compared with FF/UMEC/VI was based on a frequentist NMA.[8]

The lifetime (25 years) events in COPD patients (starting age: 65.3 years old; gender = 66% male) were based on the previously published GALAXY decision model, which used a series of linked equations derived from a three-year epidemiology study (ECLIPSE).[4] Patient characteristics from the IMPACT trial were used as the target population to populate the model.[7] The model was first developed conceptually following a systematic review of the literature on associations between disease attributes, progression, and outcomes complemented with expert knowledge elicitation.[9] Those relationships or attributes that were felt to be not quantifiable were excluded from the final conceptual model. The model assumed that lung function affects symptoms, symptoms affect exacerbations, and all three attributes affect exercise capacity. Subsequently, the ECLIPSE study of 2,164 patients was used to populate the statistical relationships for the associations defined in the concept phase.[4] The statistical relationships in the model were not necessarily all the relationships that could have been observed in the epidemiology study. The final model is composed of nine different equations predicting moderate and severe exacerbations, $FEV_1$, dyspnea (most days versus none or some), dyspnea (none versus most/several days), cough and/or sputum, six-minute walking distance (6MWD), quality-of-life score from the SGRQ-C patients, and survival. These equations used baseline predictors identified at the conceptual, phase as well as predicted values from the equations for the previous period.[4] For example, the predictive equation for moderate exacerbations is made of time in the study, the baseline and subsequent (predicted) levels of $FEV_1$ %, dyspnea, cough and/or sputum in the previous period, and the random effects and error terms.

In the third phase, pooled health care resource data from a multi-centre three-year study (TORCH) comparing FP, SAL (or FP/SAL) to placebo conducted in 444 centres (6,112 patients) across the world was used to develop predictive equations for COPD-related health care event counts such as hospital bed days (general ward, intensive care unit), emergency room visits, and outpatient visits (hospital, physician office, home at day/night). [4] [5] These equations used the baseline and follow-up levels of $FEV_1$, dyspnea, cough and

sputum, and 6MWD, and a history of exacerbations as predictors. Unit costs for the abovementioned service use categories were obtained from the following sources: drug costs from the Ontario Drug Benefit ODB Formulary,[10] and health care costs from the Canadian Institute for Health Information CIHI[11] and the Ontario Health Insurance Plan, or OHIP[12].

Finally, relative efficacy parameters of FF/UMEC/VI versus comparators were used to predict disease progression and outcomes. Treatment effects of FF/VI and UMEC/VI versus FF/UMEC/VI were based on the IMPACT trial,[7] while the treatment effect of MITT versus FF/UMEC/VI was based on an NMA.[8] Treatment effects focused on the following outcomes: change in $FEV_1$ from baseline, change in SGRQ-C from baseline, and reduction in the annual rate of moderate and severe exacerbations. These changes/reductions were then used in the risk equations to predict quality of life and costs for the comparator arms.[2]

The manufacturer's base-case analysis was conducted from the perspective of a Canadian public health care payer over a lifetime horizon, with costs and QALYs discounted at 1.5% per annum.[2]

## Manufacturer's Base Case

The manufacturer concludes from their base-case analysis that, compared with FF/VI, FF/UMEC/VI provided an additional 0.1322 QALYs at an additional cost of $2,598 per patient, with an ICUR of $19,649 per QALY and probability of 100% of being cost-effective at a willingness to pay threshold of $50,000 (Table 2).[2] The major cost driver was the higher drug cost of FF/UMEC/VI (Table 15).

When compared with UMEC/VI, FF/UMEC/VI provided an additional 0.1211 QALYs at an additional cost of $1,801 per patient, with an ICUR of $14,864 per QALY and probability of 100% of being cost-effective at a willingness to pay threshold of $50,000. The major cost driver was the higher drug cost of FF/UMEC/VI.[2]

Finally, when compared with TIO + FP/SAL 250/50 mcg and TIO + FP/SAL 500/50 mcg, costs were lower for FF/UMEC/VI (by $482 and $1,670, respectively) and benefits were comparable (FF/UMEC/VI had 0.005 and 0.028 more QALYs, respectively, over the lifetime). Based on this, FF/UMEC/VI was found to be dominant in 29.7% and 63.2% of simulations and dominated in 10.0% and 0.3% of simulations for TIO + FP/SAL 250/50 mcg and TIO + FP/SAL 500/50 mcg combinations, respectively; however, the results were associated with substantial decision uncertainty.[2]

Further details can be found in Appendix 5.

## Table 2: Summary of Results of the Manufacturer's Base Case (Probabilistic Analysis)

| | Total Costs ($) | Incremental Cost ($) | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|
| **Comparison between FF/VI and FF/UMEC/VI** | | | | | |
| FF/VI | 62,633 | | 5.1361 | | |
| FF/UMEC/VI | 65,231 | 2,598 | 5.2683 | 0.1322 | $19,649 |
| **Comparison between UMEC/VI and FF/UMEC/VI** | | | | | |
| UMEC/VI | 62,877 | | 5.1295 | | |
| FF/UMEC/VI | 64,678 | 1,801 | 5.2506 | 0.1211 | $14,864 |
| **Comparison between TIO + FP/SAL (250/50 mcg) and FF/UMEC/VI** | | | | | |
| TIO + FP/SAL (250/50 mcg) | 64,902 | | 5.1174 | | |
| FF/UMEC/VI | 64,420 | -482 | 5.1224 | 0.0050 | dominant |
| **Comparison between TIO + FP/SAL (500/50 mcg) and FF/UMEC/VI** | | | | | |
| TIO + FP/SAL (500/50 mcg) | 66,428 | | 5.1344 | | |
| FF/UMEC/VI | 64,758 | -1,670 | 5.1621 | 0.028 | dominant |

FF = fluticasone furoate; FP = fluticasone propionate; SAL = salmeterol;TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

Source: Manufacturer's Pharmacoeconomic submission.[2]

## Summary of Manufacturer's Sensitivity Analyses

A series of univariate sensitivity analyses were performed — time horizon: five and 10 years; baseline fibrinogen: 472.8 mcg per day and 482.1 mcg per day; 6MWD: 360.4 and 371.2; mMRC score ≥ 2: 27.8% and 46.3%; treatment discontinuation: 0%; hospitalization costs (ICU, Ward, emergency room costs simultaneously varied): –25% and +25%; physician visit costs (day/nighttime home visit, physician office visit, telephone consultation simultaneously varied): –25% and +25%; varying predicted utility value in each cycle; background exacerbation rate: 50% and 200% of the values obtained in the IMPACT trial; the cost of FF/VI: the utilization-weighted cost of all ICS/LABAs used for COPD ($3.5116/day and $3.2760/day instead of $2.7400/day); the cost of UMEC/VI: utilization-weighted cost of all LAMA/LABAs used for COPD ($2.417/ day instead of $2.7000/day); treatment effect for subsequent treatments: same as FF/UMEC/VI; cost of each treatment class used for subsequent therapy: assumed 100% market share of product with highest cost ($5.3125) and lowest cost ($3.1321) in each treatment class; pricing for FP/SAL dry powder inhaler: 75% and 35% of the brand price for Advair Diskus; the utilization-weighted cost of all MITTs used in Canada: $5.2527 instead of $5.0750 and $6.5039; and the discount rate: 0% and 3%.

All of these sensitivity analyses found FF/UMEC/VI to be cost-effective compared with FF/VI (ICUR ranged from $13,705 to $26,226) and UMEC/VI (ICUR ranged from $12,128 to $23,296) across all scenarios.[2]

The sensitivity analysis showed that ICURs were particularly sensitive to the assumption around relative treatment effect. When treatment effect was restricted to one of the three outcomes (i.e., $FEV_1$ only, SGRQ-C only, or exacerbations only), the ICURs increased significantly. In the case of a comparison with TIO + FP/SAL, the ICUR was also sensitive to the price assumption of FP/SAL (i.e., generic versus branded pricing).

Some results of interest include:

- For comparison of FF/UMEC/VI with TIO + FP/SAL, confidence intervals (CIs) for incremental costs and QALYs crossed zero in all sensitivity analyses, indicating a high level of uncertainty in results.
- The use of the potential generic pricing for FP/SAL led to an increase in ICUR for comparison of FF/UMEC/VI versus TIO + FP/SAL to $94,805.

## Limitations of Manufacturer's Submission

A number of key limitations were identified with the manufacturer's model. Several assumptions and structural uncertainties were not properly addressed:

- **Generalizability of the evidence to the Canadian setting.**
  The lifetime events in COPD patients are based on a series of linked risk equations derived from a three-year epidemiology study (ECLIPSE) in 2,164 patients recruited from 47 centres across the world (seven centres in Canada).[4] The health care resource use is predicted by a decision model built using the ECLIPSE study in combination with a set of resource use equations based on a multi-centre study comparing SAL, FP, FP/SAL to placebo. This later study was conducted worldwide and 16 of the 444 centres were in Canada (31% patients from Western Europe; 23% from the US; 19% from Eastern Europe; 12% from Asia-Pacific).[5] No attempt has been made to isolate information from Canadian centres or to verify that the practice patterns from these two studies are similar to those in Canada. Therefore, there is uncertainty as to how the health care resources predicted by the model are representative of the Canadian setting.
- **Choice of comparators.**
  The economic model includes a limited number of comparisons; as such, the cost-effectiveness of some routinely used and potentially important comparators is unknown. It is unclear how comparators were chosen. For instance, BUD/FOR is not included in the economic analysis but is the main comparator in the FULFIL trial, which is a pivotal study in the clinical submission. The BUD/FOR combination can be an important comparator in this case. Other dual therapy combinations, including LAMA/LABA and ICS/LABA combinations, considered appropriate by clinical experts for the management of COPD and potentially relevant to the economic analysis are listed in Table 7 and Table 8. Similarly, LAMA/LABA/ICS triple therapy combinations, other than TIO + FP/SAL, should have been considered in the economic analysis.
- **Methodological challenges in the epidemiological model.**
  A linked equation model (GALAXY) was used as the basis for the decision analysis.[3] The model uses baseline and (predicted) follow-up values of lung function, symptoms and the number of exacerbations to predict subsequent events, quality of life, and costs. One limitation is that three covariates in the GALAXY model were not available in the IMPACT study. To overcome this, the analysis substituted these covariates either with a correlated variable (i.e., mMRC grade was replaced with a cut-off based on the COPD Assessment Test, or CAT, score) or a predicted value based on a regression equation (in case of baseline fibrinogen and 6MWD). The use of predicted or correlated covariates introduces additional uncertainty in the analysis, which has not been addressed. Also, the variables used in regression models are likely to have high levels of multicollinearity, which is not dealt with or mentioned in the submission. For instance, 6MWD, $FEV_1$, and dyspnea are

likely to be correlated with each other. The epidemiological model appears to use a circular chain of equations, with lung function and symptoms at t-1 predicting exacerbations during t-1 to t, and then using the same predictors at t-1, as well as the exacerbations during t-1 to t to predict 6MWD at t. These variables are likely to be highly correlated.

- **Predictive accuracy of the epidemiology model.**
  The GALAXY model, used to predict the number of moderate and severe exacerbations using $FEV_1$, lacked accuracy in replicating the outcomes predicted by the IMPACT trial and the NMA.[2] In particular, the manufacturer's validation of the model versus the IMPACT trial results shows that the model overestimates the rate of moderate exacerbations (Model: FF/VI = 1.341, UMEC/VI = 1.341, FF/UMEC/VI = 1.146; IMPACT trial: FF/VI = 0.89, UMEC/VI = 0.97, FF/UMEC/VI = 0.75) and severe exacerbations (Model: FF/VI = 0.224, UMEC/V I= 0.224, FF/UMEC/VI = 0.197; IMPACT trial: FF/VI = 0.15, UMEC/VI = 0.19, FF/UMEC/VI = 0.13).[2] Moreover, the treatment effect on exacerbations was underestimated by the model for FF/VI and UMEC/VI and overestimated for MITT. As a result, the model predictions were adjusted in the submission to reflect the additional treatment effect observed in the trial but not predicted by the $FEV_1$ improvement. Next, treatment effects of FF/UMEC/VI on $FEV_1$ and exacerbations were used to estimate the difference between FF/UMEC/VI and reference treatments in the change in the SGRQ-C from baseline. This difference in predicted change was again adjusted to reflect the trial findings.

  The above-mentioned approach suggests that either GALAXY model lacks validity in terms of prediction or the IMPACT trial has a different patient group that does not fully represent the COPD population used to develop the GALAXY model, or both. Moreover, the abovementioned approach appears to focus on matching the model results to provide the same relative treatment benefit to FF/UMEC/VI as observed in the trial rather than using the model predicted outcomes.

  Overall, it is difficult to estimate the impact of better predictive accuracy on the ICUR, as it might affect the two groups differently. However, this issue with predictive accuracy increases uncertainty around the results and the conclusions that may be drawn from the analyses.

- **Use of mapped utility values instead of observed values.**
  Observed levels of quality of life and resource use values were available in the IMPACT trial but not used in the economic model. The submission states that the GALAXY model does not allow direct use of EQ-5D scores to reflect changes in quality of life as a result of changes in clinical status. If the model only allows the use of mapped utility values even in the presence of directly observed EQ-5D data, then this is a significant limitation of the model.

  Utilities in the model are derived from SGRQ-C through a mathematical algorithm based on Starkie et al., which maps SQRQ-C to EQ-5D.[6] Although the method is robust, when the authors used the algorithm on the study data used to develop and validate the algorithm, the derived utilities resulted in a reordering of treatments based on QALY gain when compared with using the utilities directly measured by the EQ-5D and, hence, a change in the decision.[6] Based on this, the authors do not recommend using the algorithm for health technology assessments, and suggest collecting direct data using preference-based instruments (such as the EQ-5D).[6] Finally, the EQ-5D

value set used to develop the algorithm was from the UK. It is unclear how this would affect the results had a Canadian value set been used.

Importantly, the IMPACT Clinical Study Report reports that, [redacted].[7] However, the IMPACT study found a statistically significant improvement in the SGRQ score in the FF/UMEC/VI arm relative to the comparators.[7] [redacted]

- **Relative treatment effect.**
  The treatment effect of FF/UMEC/VI versus FF/VI and UMEC/VI were based only on the IMPACT trial and not the NMA, which had the primary objective to compare FF/UMEC/VI with MITT, although it included comparisons with dual therapies. We note that evidence from the IMPACT trial was used in the NMA, and the resulting estimates for dual therapies have larger uncertainty intervals than those observed in the IMPACT trial.8 As a result, using NMA estimates for dual therapy in the decision model will have increased uncertainty in ICUR for FF/UMEC/VI compared with FF/VI and UMEC/VI.

  The NMA also had limitations [redacted]

*Other Limitations*

- **Comparator cost.**
  The results of the comparison with MITT triple therapy is largely driven by the cost of FP/SAL. The base case of the manufacturer's economic analysis uses the brand price of FP/SAL. Sensitivity analysis assuming that the generic drug would cost 75% of the branded FP/SAL led to an increase in ICUR for the comparison of FF/UMEC/VI versus TIO + FP/SAL to $94,805. In reality, a generic entrant would cost significantly less and would make FF/UMEC/VI even less cost-effective.

- **Transparency of the model.**
  The linked equation model offers limited possibilities to test other values (e.g., health utilities) to understand the full impact of certain variables.

## CADTH Common Drug Review Reanalyses

A number of limitations in manufacturer's submission could not be addressed in CADTH reanalyses, including limitations of the statistical analysis of the epidemiological study, predictive inaccuracy of the decision model, imprecision of the utility mapping algorithm, non-inclusion of other relevant comparators, and limiting the treatment effect estimation to a single trial.

CADTH conducted the following analyses to account for the limitations that could be addressed:

1. To account for generic entrants, the price of FP/SAL was assumed to be equivalent to BUD/FOR using the following approach:
    - Based on the price of BUD/FOR in the manufacturer's submission, the price of FP/SAL 250/50 mcg was assumed to be $2.2273 (instead of $3.301; i.e., a 22.5% price reduction) and the price of FP/SAL 500/50 mcg was assumed to be $2.8943 (instead of $4.686; i.e., a 38.2% price reduction)
    - For FP/SAL + LAMA combinations used as subsequent treatment, the price was assumed to be $3.894; i.e., the same as the cheapest BUD/FOR + LAMA combination in the manufacturer's submission (i.e., a 33.4% reduction).
2. The physician home visits cost was assumed to be the same as the physician office visit cost (i.e., $77.2).
3. CADTH base case (1 + 2).

Scenario analyses:

A. CADTH scenario analyses for FF/VI and UMEC/VI
    A1. Scenario 1: Price reduction of branded FP/SAL by 75% to account for potential generic entrants
    A2. Scenario 2: Cost of emergency room visit updated to $486 based on the estimate of Canadian Institute of Health Information [Note: the submission uses $76.9, which is even lower than the physician office visit cost of $77.20].
B. CADTH scenario analyses for TIO + FP/SAL (250/50 mcg and 500/50 mcg doses)
    B1. Scenario 1: Price reduction analyses of CADTH base case (where relevant)
    B2. Scenario 2: Same as scenario 1 for FF/VI and UMEC/VI
    B3. Scenario 3: Same as scenario 2 for FF/VI and UMEC/VI.

In the CADTH base-case analysis, the ICUR for FF/UMEC/VI was $21,189 per QALY compared with FF/VI (Table 3) and $17,022 per QALY compared with UMEC/VI (Table 4), with 0% of iterations showing FF/UMEC/VI being dominant (i.e., more effective, less expensive) or dominated (i.e., less effective, more expensive) in both comparisons.

The results for FF/VI and UMEC/VI comparisons were sensitive to the price of FP/SAL but generally stable across CADTH scenario analyses. Scenario 1 investigates the impact of a lower expected cost of generic FP/SAL, as the drug is now off-patent. The results show that the ICUR increased to $25,509 and $33,763 for comparison with FF/VI and UMEC/VI, respectively, when the cost of FP/SAL was reduced by 75%. Scenario 2 had little impact on the results, with the ICUR being $21,272 and $26,213 for comparisons with FF/VI and UMEC/VI, respectively.

## Table 3: CDR Reanalysis for FF/UMEC/VI Versus FF/VI

| | Scenario | ICUR | Incremental Costs | Incremental QALY | % Iterations Where FF/UMEC/VI Dominates | % Iterations Where FF/VI Dominates |
|---|---|---|---|---|---|---|
| **1** | Generic FP/SAL at same price as BUD/FOR | $21,286 | $2,799 | 0.131 | 0% | 0% |
| **2** | Physician home visit cost assumed same as office visit cost | $19,740 | $2,595 | 0.131 | 0% | 0% |
| **3** | **CADTH base case (1 + 2)** | $21,189 | $2,793 | 0.132 | 0% | 0% |
| **Scenario analyses** | | | | | | |
| **A1** | CADTH base case (3)<br>Generic FP/SAL at 25% of brand price | $25,509 | $3,363 | 0.132 | 0% | 0% |
| **A2** | CADTH base case (3)<br>Cost of emergency visit based on Canadian Institute for Health Information estimate | $21,272 | $2,799 | 0.132 | 0% | 0% |

## Table 4: CDR Reanalysis for FF/UMEC/VI Versus UMEC/VI

| | Scenario | ICUR | Incremental Costs | Incremental QALY | % Iterations Where FF/UMEC/VI Dominates | % Iterations Where UMEC/VI Dominates |
|---|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | $17,028 | $2,067 | 0.121 | 0% | 0% |
| 2 | Physician home visit cost assumed same as office visit cost | $14,874 | $1,810 | 0.122 | 0% | 0% |
| **3** | **CADTH base case (1+2)** | $17,022 | $2,065 | 0.121 | 0% | 0% |
| **Scenario analyses** | | | | | | |
| **A1** | CADTH base case (3)<br>• Generic FP/SAL at 25% of brand price | $33,763 | $3,247 | 0.096 | 0% | 0% |
| **A2** | CADTH base case (3)<br>• Cost of emergency visit based on Canadian Institute for Health Information estimate | $26,213 | $2,501 | 0.095 | 0% | 0% |

The comparison of FF/UMEC/VI and TIO + FP/SAL was highly unstable (i.e., results varying in probabilistic analyses). The ICUR in the CADTH base-case analysis was $137,990 compared with TIO + FP/SAL 250/50 mcg, with 9% of iterations showing that FF/UMEC/VI was dominant and 21.2% iterations showing that TIO + FP/SAL 250/50 mcg was dominant (Table 5). When compared with TIO + FP/SAL 500/50 mcg, the CADTH base-case analysis found FF/UMEC/VI to be dominant but with substantial uncertainty, with 24% of iterations showing FF/UMEC/VI was dominant and 8.4% iterations showing TIO + FP/SAL 500/50 mcg was dominant (Table 6).

Results of the scenario analyses for TIO +FP/SAL comparisons were also unstable and with large uncertainty intervals. As expected, reducing the price of FF/UMEC/VI by 5%, 10%, and 15% reduced the ICUR for both TIO + FP/SAL 250/50 and TIO + FP/SAL 500/50 doses. When the price was reduced by 15%, FF/UMEC/VI became the dominant option for both doses (although with large uncertainty). Price reduction increased the proportion of simulations where FF/UMEC/VI was the dominant option (FF/UMEC/VI dominance

increased from 9% in the CADTH base case to 25.8% when the price was reduced by 15% in the TIO + FP/SAL 250/50 comparison, while it increased from 24.0% to 49.1% dominant simulations for the same comparison with TIO + FP/SAL 500/50).

Scenario analyses for TIO + FP/SAL comparisons showed that the results were highly sensitive to the price of FP/SAL. When the price was reduced by 75%, the ICUR for FF/UMEC/VI increased to $946,575 and $78,274, respectively, for TIO + FP/SAL 500/50 mcg and TIO + FP/SAL 500/50 mcg comparisons. Also, TIO + FP/SAL had higher probability of being the dominant option at both doses. Finally, the scenario analysis based on higher emergency room cost had only a small impact on the ICUR compared with the CADTH base case.

Detailed information on the CADTH reanalyses can be found in Appendix 5 (CDR Reanalyses).

## Table 5: CADTH Common Drug Review Reanalysis for FF/UMEC/VI Versus TIO + FP/SAL (250/50 mcg)

| | Scenario | ICUR | Incremental Costs | Incremental QALY | % Iterations Where FF/UMEC/VI Dominates | % Iterations Where TIO + FP/SAL (250/50) Dominates |
|---|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | $197,969 | $632 | 0.003 | 9.0% | 20.7% |
| 2 | Physician home visit cost assumed same as office visit cost | Dominant | –$485 | 0.002 | 29.9% | 10.6% |
| 3 | CADTH base case (1+2) | $137,990 | $674 | 0.005 | 9.0% | 21.2% |
| **Scenario analyses** | | | | | | |
| **B1** | CADTH base case (scenario 3)<br>5% price reduction | $82,562 | $354 | 0.004 | 13.6% | 17.9% |
| | 10% price reduction | $28,584 | $76 | 0.003 | 19.4% | 15.9% |
| | 15% price reduction | Dominant | –$317 | 0.001 | 25.8% | 11.7% |
| **B2** | CADTH base case<br>• Generic FP/SAL price reduction by 75% of brand | $946,575 | $2,023 | 0.002 | 0.3% | 37.5% |
| **B3** | CADTH base case (scenario 3)<br>• Cost of emergency visit based on Canadian Institute for Health Information | $128,377 | $628 | 0.005 | 9.9% | 21.3% |

## Table 6: CADTH Common Drug Review Reanalysis for TIO + FP/SAL (500/50 mcg) Versus FF/UMEC/VI

| | Scenario | ICUR | Incremental Costs | Incremental QALY | % Iterations Where FF/UMEC/VI Dominates | % Iterations Where TIO + FP/SAL (250/50 mcg) Dominates |
|---|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | $382 | $8 | 0.022 | 23.7% | 9.2% |
| 2 | Physician home visit cost assumed same as office visit cost | Dominant | –$1,698 | 0.023 | 60.5% | 0.4% |
| 3 | CADTH base case (1 + 2) | Dominant | –$34 | 0.022 | 24.0% | 8.4% |
| **Scenario analyses** | | | | | | |
| **B1** | CADTH base case – price<br>• Not applicable | | | | | |
| **B2** | CADTH base case<br>• Generic FP/SAL price reduction by 75% of brand | $78,274 | $1,604 | 0.020 | 0.2% | 32.3% |
| **B3** | CADTH base case (3)<br>• Cost of emergency visit based on Canadian Institute for Health Information | $370 | $8 | 0.022 | 22.8% | 9.6% |

## Patient Input

Patient input was received from one patient group: COPD Canada. COPD Canada collected information from Canadian patients who indicated that COPD has a profound effect on patients' lives, as well as their caregivers. It affects aspects of daily living, resulting in issues with work, as well as normal daily activities (e.g., changing bed sheets, bathing and dressing, climbing stairs, and shopping). As the disease progresses, patients become less physically active and more socially isolated. Patients may also require the assistance of informal caregivers, which could result in caregiver fatigue, and emotional and mental strain. Specifically with respect to FF/UMEC/VI, although none of the surveyed patients had direct experience with the drug, the expectation was that it may improve compliance if it is simpler to use, has three medications in one dosage, and is used only once per day.

While activities of daily living were not specifically considered by the manufacturer, the manufacturer considered efficacy based on exacerbations and the SGRQ-C mapped to utility values. Patient adherence to treatment and caregiver burden were not considered by the manufacturer in their analysis.

## Conclusions

The model submitted by the manufacturer had a number of limitations and structural uncertainties that could not be fully tested in scenario analyses. These included the suboptimal performance of the predictive linked equations, use of mapped utilities instead of the directly observed EQ-5D data, relative efficacy based on a single trial, and, generalizability of data to the Canadian setting. Furthermore, the complexity of the model limits the possibility to test other datasets or values (e.g., health utilities).

The CADTH reanalyses, when accounting for the potential generic entrant for FP/SAL, suggest an ICUR of $21,189 per QALY for FF/UMEC/VI compared with FF/VI and $17,022 per QALY compared with UMEC/VI. This reanalysis does not, however, overcome the above-mentioned limitations of the model.

For comparison with TIO + FP/SAL 250/50 mcg, the ICUR for FF/UMEC/VI was $137,990 per QALY but FF/UMEC/VI was dominant when compared with TIO + FP/SAL 500/50 mcg. The ICURs for TIO + FP/SAL comparisons were, however, unstable and associated with substantial uncertainty. Moreover, the sensitivity analyses show that FF/UMEC/VI could be dominated by TIO + FP/SAL (i.e., less effective, more expensive) if the generic price for FP/SAL is 25% of the branded price.

# Appendix 1: Cost Comparison

The comparators presented in the table that follows have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing product listing agreements are not reflected in the table and therefore may not represent the actual costs to public drug plans.

## Table 7: CDR Cost Comparison Table for Bronchodilator Therapies for COPD

| Drug/Comparator | Strength | Dosage Form | Price ($) | Price/ Dose ($) | Recommended Dose | Average Daily Drug Cost ($) | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|---|---|
| **Fluticasone furoate/ umeclidinium/vilanterol (Trelegy Ellipta)** | **100/62.5/ 25 mcg** | **Inhalant powder (30 doses)** | **132.2000[a]** | **4.4067** | **100/62.5/25 mcg daily** | **4.41** | **1,608** |
| **Long-Acting Beta-2-Agonists /Long-Acting Muscarinic Antagonist Fixed-Dose Combinations** | | | | | | | |
| Indacaterol/glycopyrronium (Ultibro Breezhaler) | 110/50 mcg | Inhalant powder capsule | 2.6800 | 2.6800 | 110/50 mcg daily | 2.68 | 978 |
| Umeclidinium/vilanterol (Anoro Ellipta) | 62.5/25 mcg | Inhalant powder (30 doses) | 81.0000 | 2.7000 | 62.5/25 mcg daily | 2.70 | 986 |
| Aclidinium/formoterol (Duaklir Genuair) | 400/12 mcg | Inhalant powder (60 doses) | 60.0000 | 1.0000 | 400/12 mcg twice daily | 2.00 | 730 |
| **Inhaled Corticosteroid/Long-Acting Beta-2-Agonists Fixed-Dose Combinations** | | | | | | | |
| Budesonide/formoterol (Symbicort Turbuhaler) | 100/6 mcg[c] 200/6 mcg | Inhalant powder (120 doses) | 66.8200 86.8300 | 0.5568 0.7236 | 400/12 mcg twice daily | 2.89 | 1,056 |
| Fluticasone furoate/ vilanterol trifenatate (Breo Ellipta) | 100/25 mcg | Inhalant powder (30 doses) | 82.2000 | 2.7400 | 100/25 mcg once daily | 2.74 | 1,000 |
| Fluticasone propionate/ Salmeterol (Advair Diskus) | 100/50 mcg[c] 250/50 mcg 500/50 mcg | Inhalant powder (60 doses) | 82.7340 99.0360 140.5920 | 1.3789 1.6506 2.3422 | 250/50 mcg or 500/50 mcg twice daily | 3.30 to 4.68 | 1,205 to 1,710 |
| **Long-Acting Muscarinic Antagonist** | | | | | | | |
| Aclidinium bromide (Tudorza Genuair) | 400 mcg | Inhalant powder (60 doses) | 53.1000 | 0.8850 | 400 mcg twice daily | 1.77 | 646 |
| Glycopyrronium bromide (Seebri) | 50 mcg | Inhalant powder capsule | 1.7700 | 1.7700 | 50 mcg daily | 1.77 | 646 |
| Tiotropium (Spiriva) | 18 mcg | Inhalant powder capsule | 1.7300 | 1.7300 | 18 mcg daily | 1.73 | 631 |
| Tiotropium (Spiriva Respimat) | 2.5 mcg | Inhalant solution (60 doses) | 51.9000 | 0.8650 | 2.5 mcg twice daily | 1.73 | 631 |
| Umeclidinium (Incruse Ellipta) | 62.5 mcg | Inhalant powder (30 doses) | 50.0000 | 1.6667 | 62.5 mcg once daily | 1.67 | 608 |

| Drug/Comparator | Strength | Dosage Form | Price ($) | Price/ Dose ($) | Recommended Dose | Average Daily Drug Cost ($) | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|---|---|
| **Long-Acting Beta-2-Agonists** | | | | | | | |
| Salmeterol (Serevent) | 50 mcg | Inhalant powder (60 doses) | 56.6600 | 0.9400 | 50 mcg twice daily | 1.89 | 689 |
| Formoterol (Foradil) | 12 mcg | Inhalant powder capsule | 0.8490[b] | 0.8490 | 12 mcg to 24 mcg twice daily | 1.70 to 3.40 | 620 to 1,240 |
| Indacaterol maleate (Onbrez) | 75 mcg | Inhalant powder capsule | 1.5500 | 1.5500 | 75 mcg daily | 1.55 | 566 |

All prices are from the Ontario Drug Benefit Formulary (accessed April 2018)[10] unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer submitted price.

[b] Saskatchewan formulary list price.[13]

[c] Lower doses of budesonide/formoterol (i.e., 100/6 mcg) and fluticasone propionate /salmeterol (i.e., 100/50 mcg) are not indicated for COPD.

## Table 8: CDR Cost Comparison Table for Additional Therapies for COPD

| Drug/ Comparator | Strength | Dosage Form | Price ($) | Price/ Dose ($) | Recommended Dose | Average Daily Drug Cost ($) | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|---|---|
| **Short-Acting Anticholinergic** | | | | | | | |
| Ipratropium Bromide (Atrovent) | 20 mcg | MDI (200 doses) | 19.4876 | 0.0974 | 2 × 20 mcg 3 to 4 times daily | 0.58 to 0.78 | 213 to 285 |
| **Short-Acting Beta-2-Agonist** | | | | | | | |
| Salbutamol (Ventolin, Airomir, generics) | 100 mcg | MDI (200 doses) | 5.0000 | 0.0250 | 100 mcg to 200 mcg up to 4 times daily | Up to 0.20 | Up to 73 |
| Terbutaline (Bricanyl Turbuhaler) | 0.5 mg | Inhalant powder (100 doses) | 7.9667 | 0.0797 | 0.5 mg up to 6 times daily | Up to 0.48 | Up to 174 |
| **Xanthine Bronchodilator** | | | | | | | |
| Theophylline (Uniphyl, generic) | 400 mg<br>600 mg | SR Tab<br>SR Tab | 0.3734<br>0.4524 | 0.3734<br>0.4524 | Once daily, generally 400 to 800 mg (titrated on response and serum levels) | 0.37 to 0.74 | 135 to 270 |
| **Phosphodiesterase Type 4 Inhibitor** | | | | | | | |
| Roflumilast (Daxas) | 500 mcg | tab | 2.1357[a] | 2.1357 | 500 mcg daily | 2.14 | 779 |

MDI = metered dose inhaler; SR Tab = sustained relief tablet.

NOTE: All prices are from the Ontario Drug Benefit Formulary (accessed Apr 2018) [10] unless otherwise indicated and do not include dispensing fees.

[a] Wholesale price, IQVIA DeltaPA database (April 2018).[14]

# Appendix 2: Summary of Key Outcomes

## Table 9: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is FF/UMEC/VI Relative to FF/VI or UMEC/VI?[a]

| FF/UMEC/VI Versus FF/VI or UMEC/VI | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | X | | |
| **Drug treatment costs alone** | | | | X | | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | | X | | | |
| **Incremental CE ratio or net benefit calculation** | Compared with FF/VI: $21,189 per quality-adjusted life-year<br>Compared with UMEC/VI: $17,022 per quality-adjusted life-year | | | | | |

CE = cost-effectiveness ratio; FF = fluticasone furoate; UMEC = umeclidinium; VI = vilanterol.

[a] Based on CDR reanalyses.

## Table 10: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is FF/UMEC/VI Relative to TIO + FP/SAL?[a]

| FF/UMEC/VI versus TIO + FP/SAL | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | X | | |
| **Drug treatment costs alone** | | | | X | | |
| **Clinical outcomes** | | | X | | | |
| **Quality of life** | | | X | | | |
| **Incremental CE ratio or net benefit calculation** | Compared with TIO + FP/SAL 250/50 mcg: $137,990<br>Compared with TIO + FP/SAL 500/50 mcg: Dominant | | | | | |

CE = cost-effectiveness ratio; FF = fluticasone furoate; FP = fluticasone propionate; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

[a] Based on CDR reanalyses.

# Appendix 3: Additional Information

## Table 11: Submission Quality

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | X | | |
| **Comments**<br>Prior to performing the CADTH base case, the following corrections to the manufacturer's model were done:<br>• assuming price of fluticasone propionate/salmeterol to be equivalent to budesonide/formoterol to account for generic entrants<br>• physician home visits cost assumed to be the same as physician office visit cost (i.e., $77.2).<br>The decision model relied on a set of epidemiological equations that were complex and inaccessible, and did not allow manipulation of some inputs such as utility values. | | | |
| Was the material included (content) sufficient? | X | | |
| **Comments**<br>Reviewer to provide comments if checking "poor" | None | | |
| Was the submission well organized and was information easy to locate? | X | | |
| **Comments**<br>Reviewer to provide comments if checking "poor" | None | | |

## Table 12: Authors Information

**Authors of the Pharmacoeconomic Evaluation Submitted to CDR**

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

| | Yes | No | Uncertain |
|---|---|---|---|
| Authors signed a letter indicating agreement with entire document | X | | |
| Authors had independent control over the methods and right to publish analysis | X | | |

# Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) is currently being reviewed by the National Institute of Health and Care Excellence NICE in the UK, with the evidence summary likely to be published on June 14, 2018.

The Scottish Medicines Consortium has recommended restricted use within National Health Service Scotland in patients with severe chronic obstructive pulmonary disease, or COPD (i.e., forced expiratory volume in one second [$FEV_1$] < 5 0% predicted normal).[16] The basis for the assessment is that FF/UMEC/VI costs less than inhalers containing FF/VI (as trifenatate) 92 micrograms/22 micrograms and UMEC 55 micrograms administered separately.

To date, the Pharmaceutical Benefits Advisory Committee (PBAC) is the only health technology assessment agency that has made a recommendation for FF/UMEC/VI (Trelegy Ellipta) for patients with moderate to severe COPD and frequent exacerbations despite maintenance therapy. PBAC advised that "Trelegy could be acceptably cost-effective if a small price advantage was negotiated over the price of currently listed LAMA/LABA FDCs, such as umeclidinium 62.5 mcg/vilanterol 25 mcg FDC, 1 inhalation once daily."[17]

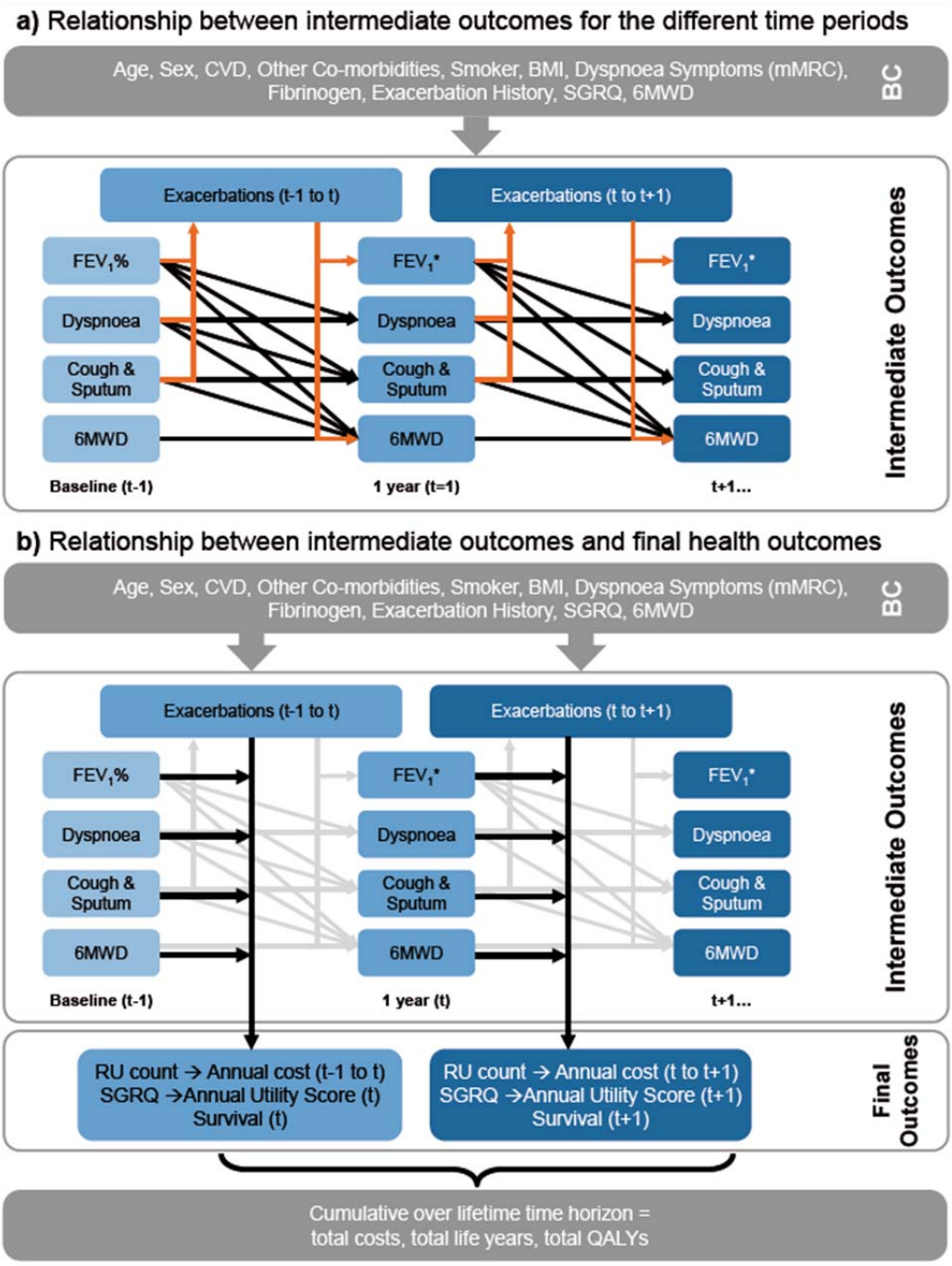
# Appendix 5: Reviewer Worksheets

## Manufacturer's Model Structure

The decision model used by the manufacturer is based on a set of linked risk equations (**Error! Reference source not found.**) derived from a large multinational, three-year epidemiology study that allowed for the prediction of disease progression according to patients' characteristics.[3,4] Model cycles are of one-year duration. The patient characteristics and the relative efficacy of FF/UMEC/VI on $FEV_1$, moderate and severe exacerbations, and quality of life measured by SGRQ-C are taken from a large, international, randomized trial. Data sources are described in Table 13, and key assumptions in Table 14.

Outcomes include $FEV_1$, moderate and severe exacerbations, St. George's Respiratory Questionnaire for COPD patients (SQRQ-C), quality-adjusted life-years (QALYs), and costs (both overall and in a disaggregated way including COPD and exacerbation medications, hospitalizations, other health care professional costs).

## Figure 1: Linked Risk Equations Model




*$FEV_1$ (mL) was calculated using the risk equation at year 't' and converted to $FEV_1$% predicted based on the cohort profile. 6MWD=six-minute walking distance; BC=baseline covariates; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; $FEV_1$=forced expiratory volume in 1 second; mMRC=modified Medical Research Council questionnaire; QALYs=quality-adjusted life years; RU=Resource Utilisation; SGRQ=St. George's Respiratory Questionnaire Total score; t=time

Source: Manufacturer's Pharmacoeconomic submission.[2]

## Table 13: Data Sources

| Data Input | Description of Data Source | Comment |
|---|---|---|
| **Efficacy** | IMPACT trial and network meta-analysis of approved therapies for COPD in Canada.[7,8] | Relative treatment effects of dual therapies (FF/VI and UMEC/VI) were based on the pivotal IMPACT trial only. However, [redacted] Moreover, dual therapy with BUD/FOR, which was the comparator in the pivotal trial FULFIL, was not included in the cost-effectiveness analysis. |
| **Natural history** | Multinational epidemiology study[4] | Only a small number (7/47) of the trial centres was from Canada. This study is used to develop linked risk equations to project disease progression and events in the economic model. |
| **Utilities** | Obtained through mapping of a disease-specific quality of life instrument.[6] | Although the methods used by Starkie et al. to develop the transformation of disease-specific quality of life data into utilities are robust, the resulting algorithm was found to be less accurate, which, in the case of the study data used to develop and validate the algorithm, resulted in a different ordering of treatments based on QALYs.[6] The EQ-5D value set used to develop the algorithm was from the UK. Using a Canadian value set might have given a different equation. Finally, the argument for not using the EQ-5D values observed in the IMPACT study is not convincing, particularly given that change in EQ-5D in the trial was similar across treatment arms. |
| **Resource use** | • Epidemiology model and FP/SAL large worldwide randomized controlled trial[5]<br>• COPD subsequent medication usage: from Ontario IMS Brogan RxDynamics® database 2017[18]<br>• Medications for moderate exacerbations: 78% antibiotics; 73% oral corticosteroids from IMPACT trial. | Only a small portion (16/444) of the trial centres used to inform resource use was from Canada. No attempt was made to isolate data for Canadian centres or validate the information for the Canadian setting. |
| **Adverse events (indicate which specific adverse events were considered in the model)** | Adverse events were not included (see manufacturer's key assumption in Table 14). | There is a slight imbalance between groups in terms of AEs, particularly between FF/UMEC/VI and UMEC/VI. Rates of any SAEs and fatal SAEs were higher in the UMEC/VI group (any SAE = 443.4; fatal SAE = 38.3) compared with FF/UMEC/VI (any SAE: 431.8; fatal SAE: 26.4). Also, 43% of the FF/UMEC/VI patients (858.2 per 1,000 subject years) versus 38% of UMEC/VI patients (797.9 per 1,000 subject years) had infections and infestations. |
| **Mortality** | Risk equation developed from the epidemiology trial[4] | |
| **Costs** | Canadian Institute for Health Information 2016 and OHIP 2016 | The price of Trelegy Ellipta ($132.20 for a pack of 30) is higher than the total price of its individual components ($119.58). More specifically, for a pack of 30, UMEC/VI (62.5/25 mcg), available as Anoro Ellipta, is priced at $81.00, while FF (100 mcg), available as Arnuity Ellipta, is priced at $38.58.<br><br>The cost of daytime and nighttime home visits are $45.15 (based on OHIP 2016 Schedule of Benefits). This is lower than the cost of a visit to a physician's office ($77.2). |
| **Drug** | Medications: Ontario Drug Benefit Formulary 2017[10] | |
| **Event** | • Medications to treat moderate | The manufacturer uses $76.90 for an ER visit based on OHIP |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| | exacerbations: Ontario Drug Benefit Formulary 2017[10]<br>• Hospital day (intensive care unit and general ward): Canadian Institute for Health Information 2016[11]<br>• ER visit, outpatient visit, home visit, office visit: OHIP 2016[11]<br>• Telephone consultation: assumption: 10-minute duration; 60% nurse: 40% physician: OHIP 2016: pay scale; Statistics Canada[19] | 2016. This value appears low in view of the value reported in the Canadian Institute for Health Information database.[20] |

AE = adverse event; BUD = budesonide; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQuol 5-Dimensions questionnaire; ER = emergency room; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; QALY = quality-adjusted life-year; SAE = serious adverse event; UMEC = umeclidinium; VI = vilanterol (VI).

## Table 14: Manufacturer's Key Assumptions

| Assumption | Comment |
|---|---|
| The characteristics of the COPD population included in the IMPACT trial were similar to the population expected to be treated with FF/UMEC/VI in Canada. | It is not clear if this assumption has been explicitly assessed against any Canadian studies. |
| It was assumed the disease progression from the GALAXY risk equations, adjusted to the IMPACT patient characteristics, represents that of patients receiving the reference treatment (FF/VI, UMEC/VI, TIO + FP/SAL 250/50 or TIO + FP/SAL 500/50). Relative treatment effect for FF/UMEC/VI as observed in the IMPACT trial (compared with the reference treatment) was applied in the model to adjust values for risk equation variables; this predicted disease progression in the FF/UMEC/VI arm. | Uncertain. Predicted outcomes from the GALAXY model were adjusted to reflect the treatment effect observed in the IMPACT trial. |
| The duration of FF/UMEC/VI treatment observed in the IMPACT trial was assumed to continue for as long as the patients continue to receive treatment in the model; i.e., until discontinuation. | Uncertain. |
| The treatment effect of FF/UMEC/VI in the model was assumed to be as observed in the trial until discontinuation of treatment. | Uncertain. This was based only on the IMPACT trial and not on the network meta-analysis, which produced estimates with larger uncertainty intervals. |
| In the development of the GALAXY model risk equations, the lagged value (value in the prior time period, t-1) for $FEV_1$% predicted was needed in order to calculate the first predicted outcome of the dyspnea risk equations. For the baseline prediction of the proportion estimates for the dyspnea and cough and/or sputum equations, the lagged value for $FEV_1$% predicted (i.e., one year before baseline) is not known. Therefore, it was assumed the $FEV_1$% predicted at baseline was the lagged $FEV_1$% predicted. | Uncertain. |
| The metrics of disease progression can be captured appropriately in a one-year cycle length. | Appropriate |
| The frequency of adverse events leading to discontinuation from treatment was captured in the data describing discontinuation and not modelled separately. | Appropriate |

| Assumption | Comment |
|---|---|
| Adverse events were not explicitly modelled in this analysis. Adverse event type and frequency were assumed not to be significantly different between arms in the IMPACT trial, and would therefore not affect results for the modelled comparisons. | There is slight imbalance between groups in terms of AEs, particularly between FF/UMEC/VI and UMEC/VI. Rates of any SAEs and fatal SAEs were higher in UMEC/VI group (any SAE = 443.4; fatal SAE = 38.3) compared with FF/UMEC/VI (any SAE: 431.8; fatal SAE: 26.4). Also, 43% of the FF/UMEC/VI patients (858.2 per 1,000 subject years) versus 38% of UMEC/VI patients (797.9 per 1,000 subject years) had infections and infestations. |
| Discontinuation in subsequent years was assumed same as first year in the reference case. This was a conservative approach and may overestimate discontinuation in subsequent years. Sensitivity analyses were conducted using an annual discontinuation rate of 0% in subsequent years.<br><br>Patients who discontinued FF/UMEC/VI treatment were assumed to have the same efficacy as the reference treatment (dual combination, i.e., FF/VI or UMEC/VI, or MITT [TIO + FP/SAL]) for the remaining duration of the analysis. Patients who discontinue reference treatment (FF/VI, UMEC/VI, or MITT) were assumed to not have any change in their efficacy. These assumptions were tested in the sensitivity analyses, where patients who discontinued FF/UMEC/VI treatment were assumed to not have any change in their efficacy and patients discontinued reference treatment (FF/VI, UMEC/VI, or MITT) were assumed to have the same efficacy as FF/UMEC/VI for the remaining duration of the analysis.<br><br>Treatment patterns for subsequent therapy after discontinuation from the study treatment would be similar to the treatment patterns in the Canadian population. | Appropriate |

AE = adverse event; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiration volume in one second; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; MITT = multiple inhaler triple therapy; SAE = serious adverse event; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol (VI).

## Manufacturer's Results

In the manufacturer's base-case analysis, the ICUR for FF/UMEC/VI was $19,649 (95% CI $15,406, $26,454) and $14,864 (95% CI $11,151, $20,850) for FF/VI and UMEC/VI, respectively. Lifetime incremental costs reached $2,598 and $1,801, while the QALY gain was 0.1322 and 0.1211, respectively against FF/VI and UMEC/VI. When compared with TIO + FP/SAL 250/50 mcg and TIO + FP/SAL 500/50 mcg, costs were lower for FF/UMEC/VI ($482 and $1,670, respectively) and benefits were comparable (FF/UMEC/VI had 0.005 and 0.028 more QALYs, respectively, over the lifetime). Based on this, FF/UMEC/VI was found to be dominant in 29.7% and 63.2% of simulations, and dominated in 10.0% and 0.3% of simulations for TIO + FP/SAL 250/50 mcg and TIO + FP/SAL 500/50 mcg combinations, respectively. The tables from the manufacturer's pharmacoeconomic evaluation showing the detailed results of the manufacturer's base case are reproduced in Table 15.

The manufacturer's submission also included a number of scenario analyses, but the choice of parameters and assumptions produced similar results to the base case in most scenarios. However, using generic pricing for FP/SAL led to an increase in ICUR for the comparison of FF/UMEC/VI versus TIO + FP/SAL to $94,805. We note that many key limitations of the base-case analysis were not explored in the scenario analyses.

## Table 15: Manufacturer's Base Case Results — FF/UMEC/VI Versus FF/VI

| | FF/VI | FF/UMEC//VI | Incremental |
|---|---|---|---|
| **Cumulative exacerbations** | | | |
| Moderate exacerbations | 11.1270 | 10.5233 | -0.6037 |
| Severe exacerbations | 3.4781 | 3.3830 | -0.0951 |
| Total exacerbations (moderate and severe) | 14.6051 | 13.9064 | -0.6987 |
| Moderate exacerbations PPPY | 1.2407 | 1.1549 | -0.0858 |
| Severe exacerbations PPPY | 0.3860 | 0.3695 | -0.0164 |
| Total exacerbations PPPY | 1.6267 | 1.5244 | -0.1023 |
| **Health Outcomes** | | | |
| Accumulated LYs (undiscounted) | 8.9700 | 9.1093 | 0.1392 |
| Accumulated QALYs | 5.1361 | 5.2683 | 0.1322 |
| **Costs** | | | |
| Accumulated costs total | $62,633 | $65,231 | $2,598 |
| Drug costs | $11,532 | $13,461 | $1,929 |
| Total non-drug costs | $51,101 | $51,770 | $669 |
| Hospital (ICU and ward) costs | $49,880 | $50,543 | $662 |
| Outpatient/ER costs | $632 | $638 | $5.51 |
| Physician visit (office, home day/night) costs | $589 | $590 | $0.99 |
| **Incremental Results** | | | |
| Incremental costs (95% CI), | | $2,598 | ($2,010, $3,268) |
| Incremental LYs (95% CI) undiscounted | | 0.1392 | (0.07, 0.21) |
| Incremental QALYs (95% CI) | | 0.1322 | (0.09, 0.18) |
| ICER /QALY gained (95% CI) | | **$19,649** | **($15,406, $26,454)** |

*Abbreviations: ER= emergency room; FF = fluticasone furoate; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LY = life years; PPPY = per patient per year; QALY = quality adjusted life year; UMEC = umeclidinium bromide; VI = vilanterol*

Source: Manufacturer's pharmacoeconomic submission.[2]

## Table 16: Manufacturer's Base Case Results — FF/UMEC/VI Versus UMEC/VI

| | UMEC/VI | FF/UMEC//VI | Incremental |
|---|---|---|---|
| **Cumulative exacerbations** | | | |
| Moderate exacerbations | 11.1232 | 10.1632 | -0.9600 |
| Severe exacerbations | 3.4799 | 3.1280 | -0.3519 |
| Total exacerbations (moderate and severe) | 14.6031 | 13.2911 | -1.3120 |
| Moderate exacerbations PPPY | 1.2415 | 1.1189 | -0.1226 |
| Severe exacerbations PPPY | 0.3866 | 0.3426 | -0.0440 |
| Total exacerbations PPPY | 1.6280 | 1.4615 | -0.1665 |
| **Health Outcomes** | | | |
| Accumulated LYs (undiscounted) | 8.9612 | 9.0772 | 0.1160 |
| Accumulated QALYs | 5.1295 | 5.2506 | 0.1211 |
| **Costs** | | | |
| Accumulated costs total | $62,877 | $64,678 | $1,801 |
| Drug costs | $11,585 | $13,411 | $1,825 |
| Total non-drug costs | $51,292 | $51,267 | -$24.9 |
| Hospital (ICU and ward) costs | $50,070 | $50,048 | -$21.6 |
| Outpatient/ER costs | $635 | $634 | -$0.63 |
| Physician visit (office, home day/night) costs | $588 | $585 | -$2.63 |
| **Incremental Results** | | | |
| Incremental costs (95% CI), | | $1,801 | ($1,225, $2,316) |
| Incremental LYs (95% CI) undiscounted | | 0.1160 | (0.05, 0.19) |
| Incremental QALYs (95% CI) | | 0.1211 | (0.08, 0.17) |
| ICER /QALY gained (95% CI) | | **$14,864** | **($11,151, $20,850)** |

*Abbreviations: ER = emergency room; FF = fluticasone furoate; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LY = life years; PPPY = per patient per year; QALY = quality adjusted life year; UMEC = umeclidinium bromide; VI = vilanterol*

Source: Manufacturer's pharmacoeconomic submission.[2]

## Table 17: Manufacturer's Base Case Results — FF/UMEC/VI Versus TIO + FP/SAL 250/50

| | TIO + FP/SAL 250/50 | FF/UMEC/VI | Incremental |
|---|---|---|---|
| **Cumulative exacerbations** | | | |
| Moderate exacerbations | 11.0824 | 11.2286 | 0.1462 |
| Severe exacerbations | 3.4653 | 3.4916 | 0.0263 |
| Total exacerbations (moderate and severe) | 14.5477 | 14.7202 | 0.1725 |
| Moderate exacerbations PPPY | 1.2400 | 1.2578 | 0.0178 |
| Severe exacerbations PPPY | 0.3858 | 0.3885 | 0.0027 |
| Total exacerbations PPPY | 1.6258 | 1.6464 | 0.0205 |
| **Health Outcomes** | | | |
| Accumulated LYs (undiscounted) | 8.9387 | 8.9464 | 0.0077 |
| Accumulated QALYs | 5.1174 | 5.1224 | 0.0050 |
| **Costs** | | | |
| Accumulated costs total | $64,902 | $64,420 | -$482 |
| Drug costs | $13,864 | $13,238 | -$626 |
| Total non-drug costs | $51,038 | $51,182 | $144 |
| Hospital (ICU and ward) costs | $49,819 | $49,959 | $140 |
| Outpatient/ER costs | $631 | $633 | $2 |
| Physician visit (office, home day/night) costs | $588 | $589 | $2 |
| **Incremental Results** | | | |
| Incremental costs (95% CI) | | -$482 | (-$3,645, $2,874) |
| Incremental LYs (95% CI) undiscounted | | 0.008 | (-0.300, 0.270) |
| Incremental QALYs (95% CI) | | 0.005 | (-0.203, 0.183) |
| ICER /QALY gained (95% CI) | | **Dominant** | |
| Simulations leading to FF/UMEC/VI being dominant | | | **29.7%** |
| Simulations leading to FF/UMEC/VI being dominated | | | **10.0%** |

*Abbreviations: CI = confidence interval; ER= emergency room; FP = fluticasone propionate; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LY = life years; PPPY = per patient per year; QALY = quality adjusted life year; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium bromide; VI = vilanterol*

Source: Manufacturer's pharmacoeconomic submission.[2]

## Table 18: Manufacturer's Base Case Results — FF/UMEC/VI Versus TIO + FP/SAL 500/50

| | TIO + FP/SAL 500/50 | FF/UMEC/VI | Incremental |
|---|---|---|---|
| **Cumulative exacerbations** | | | |
| Moderate exacerbations | 11.1301 | 10.8753 | -0.2547 |
| Severe exacerbations | 3.4808 | 3.4344 | -0.0464 |
| Total exacerbations (moderate and severe) | 14.6109 | 14.3097 | -0.3012 |
| Moderate exacerbations PPPY | 1.2412 | 1.2080 | -0.0332 |
| Severe exacerbations PPPY | 0.3862 | 0.3795 | -0.0067 |
| Total exacerbations PPPY | 1.6274 | 1.5875 | -0.0399 |
| **Health Outcomes** | | | |
| Accumulated LYs (undiscounted) | 8.9694 | 9.0076 | 0.0382 |
| Accumulated QALYs | 5.1344 | 5.1621 | 0.0277 |
| **Costs** | | | |
| Accumulated costs total | $66,428 | $64,758 | -$1,670 |
| Drug costs | $15,163 | $13,318 | -$1,844 |
| Total non-drug costs | $51,266 | $51,440 | $174 |
| Hospital (ICU and ward) costs | $50,041 | $50,214 | $173 |
| Outpatient/ER costs | $634 | $635 | $1 |
| Physician visit (office, home day/night) costs | $590 | $590 | -$0 |
| **Incremental Results** | | | |
| Incremental costs (95% range), | | -$1,670 | (-$3,596, $251) |
| Incremental LYs (95% range) undiscounted | | 0.038 | (-0.176, 0.236) |
| Incremental QALYs (95% range) | | 0.028 | (-0.118, 0.161) |
| ICER /QALY gained (95% range) | | **Dominant** | |
| Simulations leading to FF/UMEC/VI being dominant | | | **63.2%** |
| Simulations leading to FF/UMEC/VI being dominated | | | **0.3%** |

*Abbreviations: ER = emergency room; FF = fluticasone furoate; FP = fluticasone propionate; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LY = life years; PPPY = per patient per year; QALY = quality adjusted life year; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium bromide; VI = vilanterol*

Source: Manufacturer's pharmacoeconomic submission.[2]

## CADTH Common Drug Review Reanalyses

### Table 19: FF/VI Versus FF/UMEC/VI — CDR Detailed Scenario Results

| | Element | | Total Costs | Total QALY | ICUR |
|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | FF/VI | $61,380 | 5.14 | |
| | | FF/UMEC/VI | $64,179 | 5.27 | |
| | | Incremental | $2,799 | 0.13 | $21,286 |
| 2 | Physician home visit cost assumed same as office visit cost | FF/VI | $62,748 | 5.12 | |
| | | FF/UMEC/VI | $65,344 | 5.26 | |
| | | Incremental | $2,595 | 0.13 | $19,740 |
| 3 | **CADTH base case (1 + 2)** | FF/VI | $60,948 | 5.13 | |
| | | FF/UMEC/VI | $63,742 | 5.26 | |
| | | Incremental | $2,793 | 0.13 | $21,189 |
| **Scenario analyses** | | | | | |
| **A1** | CADTH base case (3)<br>• Generic FP/SAL at 25% of brand price | FF/VI | $56,830 | 5.12 | |
| | | FF/UMEC/VI | $60,193 | 5.26 | |
| | | Incremental | $3,363 | 0.13 | $25,509 |
| **A2** | CADTH base case (3)<br>• Cost of emergency visit based on CIHI estimate | FF/VI | $61,954 | 5.13 | |
| | | FF/UMEC/VI | $64,753 | 5.26 | |
| | | Incremental | $2,799 | 0.13 | $21,272 |

BUD = budesonide; CDR = Common Drug Review; CIHI = Canadian Institute for Health Information; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SAL = salmeterol; UMEC = umeclidinium; VI = vilanterol (VI).

### Table 20: UMEC/VI Versus FF/UMEC/VI — CDR Detailed Scenario Results

| | Element | | Total Costs | Total QALY | ICUR |
|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | UMEC/VI | $61,120 | 5.12 | |
| | | FF/UMEC/VI | $63,186 | 5.25 | |
| | | Incremental | $2,067 | 0.12 | $17,028 |
| 2 | Physician home visit cost assumed same as office visit cost | UMEC/VI | $62,652 | 5.14 | |
| | | FF/UMEC/VI | $64,462 | 5.26 | |
| | | Incremental | $1,810 | 0.12 | $14,874 |
| 3 | **CADTH base case (1 + 2)** | UMEC/VI | $61,173 | 5.13 | |
| | | FF/UMEC/VI | $63,238 | 5.25 | |
| | | Incremental | $2,065 | 0.12 | $17,022 |
| **Scenario analyses** | | | | | |
| **A1** | CADTH base case (3)<br>• Generic FP/SAL at 25% of brand price | UMEC/VI | $56,615 | 5.13 | |
| | | FF/UMEC/VI | $59,861 | 5.22 | |
| | | Incremental | $3,247 | 0.10 | $33,763 |
| **A2** | CADTH base case (3)<br>• Cost of emergency visit based on CIHI estimate | UMEC/VI | $61,773 | 5.12 | |
| | | FF/UMEC/VI | $64,274 | 5.22 | |
| | | Incremental | $2,501 | 0.10 | $26,213 |

BUD = budesonide; CDR = Common Drug Review; CIHI = Canadian Institute for Health Information; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SAL = salmeterol; UMEC = umeclidinium; VI = vilanterol (VI).

## Table 21: TIO + FP/SAL (250/50 mcg) Versus FF/UMEC/VI — CDR Detailed Scenario Results

| | Element | | Total Costs | Total QALY | ICUR |
|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | TIO 18 mcg + FP/SAL (250/50 mcg) | $64,062 | 5.126 | |
| | | FF/UMEC/VI | $64,694 | 5.129 | |
| | | Incremental | $632 | 0.003 | $197,969 |
| 2 | Physician home visit cost assumed same as office visit cost | TIO 18 mcg + FP/SAL (250/50 mcg) | $65,165 | 5.133 | |
| | | FF/UMEC/VI | $64,680 | 5.135 | |
| | | Incremental | −$485 | 0.002 | Dominant |
| 3 | **CADTH base case (1 + 2)** | TIO 18 mcg + FP/SAL (250/50 mcg) | $64,089 | 5.137 | |
| | | FF/UMEC/VI | $64,762 | 5.142 | |
| | | Incremental | $674 | 0.005 | $137,990 |
| **Scenario analyses** | | | | | |
| **B1** | CADTH base case (3)<br>• 5% price reduction | TIO 18 mcg + FP/SAL (250/50 mcg) | $63,942 | 5.133 | |
| | | FF/UMEC/VI | $64,296 | 5.137 | |
| | | Incremental | $354 | 0.004 | $82,562 |
| | • 10% price reduction | TIO 18 mcg + FP/SAL (250/50 mcg) | $64,007 | 5.130 | |
| | | FF/UMEC/VI | $64,083 | 5.133 | |
| | | Incremental | $76 | 0.003 | $28,584 |
| | • 15% price reduction | TIO 18 mcg + FP/SAL (250/50 mcg) | $64,029 | 5.1291 | |
| | | FF/UMEC/VI | $63,712 | 5.131 | |
| | | Incremental | -$317 | 0.001 | Dominant |
| **B2** | CADTH base case<br>• Generic FP/SAL price reduction by 75% of brand | TIO 18 mcg + FP/SAL (250/50 mcg) | $62,553 | 5.127 | |
| | | FF/UMEC/VI | $64,577 | 5.129 | |
| | | Incremental | $2,023 | 0.002 | $946,575 |
| **B3** | CADTH base case (3)<br>• Cost of emergency visit based on CIHI | TIO 18 mcg + FP/SAL (250/50 mcg) | $64,827 | 5.126 | |
| | | FF/UMEC/VI | $65,455 | 5.130 | |
| | | Incremental analysis | $628 | 0.005 | $128,377 |

BUD = budesonide; CDR = Common Drug Review; CIHI = Canadian Institute for Health Information; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol (VI).

## Table 22: TIO + FP/SAL (500/50 mcg) Versus FF/UMEC/VI — CDR Detailed Scenario Results

| | Element | | Total Costs | Total QALY | ICUR |
|---|---|---|---|---|---|
| 1 | Generic FP/SAL at same price as BUD/FOR | TIO 18 mcg + FP/SAL (500/50 mcg) | $64,505 | 5.12 | |
| | | FF/UMEC/VI | $64,513 | 5.14 | |
| | | Incremental | $8 | 0.02 | $382 |
| 2 | Physician home visit cost assumed same as office visit cost | TIO 18 mcg + FP/SAL (500/50 mcg) | $66,301 | 5.14 | |
| | | FF/UMEC/VI | $64,603 | 5.16 | |
| | | Incremental | −$1,698 | 0.02 | Dominant |
| 3 | **CADTH base case (1+2)** | TIO 18 mcg + FP/SAL (500/50 mcg) | $64,607 | 5.13 | |
| | | FF/UMEC/VI | $64,573 | 5.15 | |
| | | Incremental | −$34 | 0.02 | Dominant |
| **Scenario analyses** | | | | | |
| **B1** | CADTH base case — price<br>• Not applicable | | | | |
| **B2** | CADTH base case<br>• Generic FP/SAL price reduction by 75% of brand | TIO 18 mcg + FP/SAL (500/50 mcg) | $63,204 | 5.13 | |
| | | FF/UMEC/VI | $64,809 | 5.15 | |
| | | Incremental | $1,604 | 0.02 | $78,274 |
| **B3** | CADTH base case (3)<br>• Cost of emergency visit based on CIHI | TIO 18 mcg + FP/SAL (500/50 mcg) | $65,409 | 5.13 | |
| | | FF/UMEC/VI | $65,417 | 5.15 | |
| | | Incremental | $8 | 0.02 | $370 |

BUD = budesonide; CDR = Common Drug Review; CIHI = Canadian Institute for Health Information; FF = fluticasone furoate; FOR = formoterol fumarate; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol (VI).

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