Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	umeclidinium/vilanterol (Anoro Ellipta) dry powder inhaler (DPI)
Indication	Indicated for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Listing request	List in a similar manner to tiotropium, as a maintenance bronchodilator treatment for COPD.
Manufacturer	GlaxoSmithKline Canada Inc. (GSK)

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respirology who provided input on the conduct of the review and the interpretation of findings.

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

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate
EQ-5D	EuroQol 5-Dimensions Questionnaire
FEV_1	forced expiratory volume in one second
ICS	inhaled corticosteroid
ICUR	incremental cost-utility ratio
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonist
mcg	microgram
QALY	quality-adjusted life-year
SGRQ	St. George's Respiratory Questionnaire
TORCH	TOwards a Revolution in COPD Health
UMEC	umeclidinium bromide
VI	vilanterol trifenatate

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	umeclidinium bromide/vilanterol trifenatate (Anoro Ellipta)
Study Question	"The objective of this study was to estimate the relative cost of treatment with Anoro Ellipta (UMEC/VI) compared with tiotropium in individuals with moderate to severe COPD with $FEV_1 \leq 70\%$ predicted normal (post-bronchodilator)." Although this states relative cost comparison, the analysis is in a form of a CUA, and not only a cost comparison.
Type of Economic Evaluation	CUA
Target Population	Adults with COPD, and $FEV_1 \leq 70\%$ predicted post-bronchodilator
Treatment	umeclidinium bromide/vilanterol trifenatate (Anoro Ellipta), 62.5 mcg/ 25 mcg, multi-dose dry powder inhaler
Outcomes	Life-years, QALYs, exacerbations
Comparator(s)	Tiotropium 18 mcg
Perspective	Canadian health care system
Time Horizon	20 years
Results for Base Case	UMEC/VI dominates tiotropium
Key Limitations	• Tiotropium is not considered to be the most relevant comparator to dual LAMA/LABA therapy. Other dual therapies have not been included as comparators. • Inconsistent results in clinical trials compared with tiotropium in terms of lung function parameter (FEV_1) (which is the only parameter in the model that is different among UMEC/VI and tiotropium) were observed, which increase the uncertainty regarding the efficacy inputs and further predict clinical benefits from the model. • There is no direct clinical evidence to support claims that UMEC/VI reduces COPD exacerbations, the main factor to the overall cost and quality of life for patients with COPD. • Estimated exacerbations and dyspnea are based on risk equations with FEV_1 as a predictor, which are not supported by the clinical evidence for UMEC/VI.
CDR Estimate(s)	• When compared with tiotropium, CDR reanalysis resulted in a marginal difference of $2 and 0.004 QALYs. • Tiotropium was not considered to be the most relevant comparator. The cost-effectiveness versus other dual therapies that are considered to be more relevant comparators were not provided by the manufacturer and is therefore unknown.

CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; CUA = cost-utility analysis; FEV_1 = forced expiratory volume in one second; LABA = long-acting beta2-agonists; LAMA = long-acting muscarinic antagonist; mcg = microgram; QALYs = quality-adjusted life-years; UMEC/VI = umeclidinium/vilanterol.

EXECUTIVE SUMMARY

Background

Umeclidinium bromide ("umeclidinium")/vilanterol trifenatate ("vilanterol") (UMEC/VI; Anoro Ellipta) is a long-acting muscarinic antagonist/beta2-agonist (LAMA/LABA) indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1] The recommended dose is one inhalation of 62.5 mcg/25 mcg once daily, administered through a multi-dose dry powder inhaler.

The manufacturer submitted a confidential price of [redacted] x 30 inhaled dose [redacted] per package, or [redacted] daily.

A cost-utility analysis was submitted comparing umeclidinium/vilanterol (UMEC/VI) with tiotropium 18 mcg in adult patients with moderate to severe COPD, forced expiratory volume in one second (FEV_1) ≤ 70% predicted post-bronchodilator. The economic submission is based on COPD disease progression risk equations model. The model presented a 20-year time horizon, with cycle lengths of six months, from the perspective of the public health care payer.

Summary of Identified Limitations and Key Results

The following main limitations with the manufacturer's economic model were identified:

- **Choice of comparator**: Tiotropium (LAMA monotherapy) is not considered to be the most relevant comparator to dual LAMA/LABA therapy. The comparable clinical and cost-effectiveness of UMEC/VI to existing LABA/LAMA combination therapies is unknown.
- **Inconsistent clinical evidence around lung function parameter:** Inconsistency in the results of the clinical trials of UMEC/VI versus tiotropium monotherapy in terms of lung function parameter measured as FEV_1, the primary outcome in the studies, was observed. This contributes to the uncertainty regarding the clinical benefits, and resulting cost-effectiveness, of UMEC/VI as FEV_1 is the only parameter in the model that differentiates UMEC/VI.
- **No difference in quality of life and patient-related important outcomes:** No statistically significant difference was observed in the studies between UMEC/VI and tiotropium in dyspnea or improved quality of life, or important patient-related outcomes (e.g., reduced breathlessness, use of rescue medication). Therefore, the clinical benefit predicted in the model, although marginal (incremental 0.014 quality-adjusted life-years [QALYs], which translates into five quality-adjusted days over 20 years) is very uncertain and is not supported by the clinical evidence.
- **No evidence on treatment effect on exacerbations:** Information on COPD exacerbations was not captured in the clinical trials for UMEC/VI versus tiotropium. With the growing evidence of the impact of COPD exacerbations on patients' quality of life and incurred health care costs, assessing cost-effectiveness of a COPD treatment without clinical evidence of the effect on exacerbations is a serious limitation. As a result, the manufacturer was dependent on a series of predictive equations to link FEV_1 to clinically important outcomes.
- **Estimated exacerbations and dyspnea based on risk equations with FEV_1 as a predictor:** Uncertainty exists as to whether FEV_1, as a surrogate outcome, and exacerbations and dyspnea are reliably associated. Further, where this association is established, whether the manufacturer's risk equation captures the association correctly needs to be verified. The association between FEV_1 and exacerbations and dyspnea has not been confirmed in the UMEC/VI clinical studies.

- **Risk equations based on:** Evaluation of COPD Longitudinally to Identify Predictive Surrogate (ECLIPSE) and TOwards a Revolution in COPD Health (TORCH) data. Applying the correlations derived using ECLIPSE and TORCH studies might not be appropriate, as these studies included patients on LABA plus inhaled corticosteroid (ICS) regimen, a regimen used for more severe patients experiencing exacerbations.

The CADTH Common Drug Review (CDR) undertook a scenario analysis based on the limitations identified. Excluding FEV_1 as a predictor of exacerbations and dyspnea from the risk equations resulted in a cost difference of $2 and a quality of life difference of 0.004 QALYs for UMEC/VI versus tiotropium. This marginal difference in cost and QALY resulted in an incremental cost-utility ratio (ICUR) of $702. The finding of UMEC/VI being dominant compared with tiotropium has not been maintained [redacted].

Conclusions

Based on the clinical trials for UMEC/VI, the results in terms of clinical outcomes for FEV_1 appear to be inconsistent when compared with tiotropium. This leads to uncertainty in the manufacturer's economic model in terms of the clinical benefit for UMEC/VI when FEV_1 is used to predict exacerbations and dyspnea. While UMEC/VI is priced [redacted] tiotropium, and less than other combination products, the clinical benefit of UMEC/VI compared with single drugs and other combination products has not been established based on the UMEC/VI clinical trials.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a chronic obstructive pulmonary disease (COPD) progression risk equation model with a 20-year time horizon and cycle length of one year, comparing UMEC/VI with tiotropium.

Patients moved through the model based on statistical risk equations that correlate patients' characteristics (age, sex, body mass index, comorbidities, prior exacerbation history, presence of symptoms, smoking status, fibrinogen biomarkers, St. George's Respiratory Questionnaire [SGRQ] health status, lung function and exercise capacity), the primary outcome (per cent predicted forced expiratory volume in one second [FEV_1]), the intermediate outcomes (exacerbations, cough and sputum, and six-minute walk test) and the final outcomes (costs, mortality, and quality of life) (FIGURE 1).

The statistical risk equations for the clinical end points were derived from analysis using data from the observational study Evaluation of COPD Longitudinally to Identify Predictive Surrogate (ECLIPSE).[2] The baseline parameters were derived from UMEC/VI trials where available, supplemented with data from ECLIPSE. Data on relative effectiveness among treatments was captured in terms of trough FEV_1 and were obtained from an unpublished meta-analysis from the clinical studies DB2113374, DB2113360, and ZEP117115 that included the tiotropium group. Risk equations were used to estimate SGRQ scores, which were further mapped into EuroQol 5-Dimensions Questionnaire (EQ-5D) scores based on a published algorithm.[3] The resource use was based on risk equations using data from TOwards a Revolution in COPD Health (TORCH) study[4] and the unit costs were based on Canadian sources.

2. MANUFACTURER'S BASE CASE

In the reference case, the manufacturer reported that the total cost for UMEC/VI was $30,956, a reduced cost of $153 compared with tiotropium ($31,108). Patients using UMEC/VI treatment experienced an average of 1.145 exacerbations per year, a decrease of 0.009 in comparison with tiotropium. Treatment with UMEC/VI resulted in 4.37 total quality-adjusted life-years (QALYs), an additional 0.01 QALY compared with tiotropium. Hence, the manufacturer reported that UMEC/VI dominates tiotropium (more effective, less expensive).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of UMEC/VI ($)	Total QALYs	Incremental QALYs of UMEC/VI	Incremental Cost per QALY
UMEC/VI	30,956		4.37		
Tiotropium	31,108	–$153	4.36	0.01	dominant

QALY = quality-adjusted life-year; UMEC/VI = umeclidinium bromide/vilanterol trifenatate.
Source: Manufacturer's pharmacoeconomic submission.[5]

The predicted benefit of 0.014 QALYs is marginal and translates into five quality-adjusted days over a time horizon of 20 years.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Choice of comparator:** Tiotropium is the only comparator used in the submitted model. As a long-acting muscarinic antagonist (LAMA) monotherapy, tiotropium is not considered to be the most relevant comparator to dual LAMA/long-acting beta2-agonists (LABA) therapy. A combination of tiotropium with a LABA therapy would have been a more appropriate comparator. The manufacturer has conducted an indirect treatment comparison (ITC) among UMEC/VI and tiotropium plus indacaterol, fluticasone/salmeterol plus tiotropium or QVA149; however, the results were not used in the economic submission. The CADTH Common Drug Review (CDR) reviewed the ITC and identified numerous limitations in the CDR clinical report. Therefore, the comparable clinical and cost-effectiveness of UMEC/VI to existing LABA/LAMA combination therapies remains unknown.
- **Inconsistent clinical evidence in tiotropium-controlled clinical trials:** Only one of the three tiotropium-controlled studies showed a statistically and clinically significant difference in favour of UMEC/VI in terms of trough FEV_1 as a primary clinical outcome. For secondary outcomes, no statistically or clinically significant improvements were demonstrated with UMEC/VI with regard to dyspnea. The differences were not always significant in terms of the important patient-related outcomes (reduced breathlessness, use of rescue medication, and improved quality of life) as well. Therefore, there is large inconsistency in the results of the dual therapy with UMEC/VI versus tiotropium monotherapy, which further contributes to the uncertainty regarding the cost-effectiveness of UMEC/VI.
- **Quality of life:** Statistically significant difference in quality of life measured in terms of SGRQ was not achieved in two out of three trials (DB2113374, DB2113360) comparing UMEC/VI with tiotropium. The one trial (ZEP117115) that resulted in a statistically significant difference did not result in a clinically significant difference. The positive difference captured in the model, although marginal (incremental 0.014 QALYs over the life horizon, which translates into five quality-adjusted days over a time horizon of 20 years), is very uncertain, as it is not supported by the clinical evidence.
- **No evidence of treatment effect on exacerbations:** The submitted model incorporates least squares mean difference for trough FEV_1 (in millilitres) as the only treatment effect of UVEC/VI and tiotropium. Exacerbations are known to have major impact on the quality of life of COPD patients, as they contribute considerably to morbidity and mortality.[6] There is no clinical evidence to measure the difference between UMEC/VI and tiotropium in this sense. Moreover, COPD exacerbations are one of the main factors affecting the overall cost related to COPD treatment, as it has been reported that the greatest proportion of direct medical costs are attributable to hospital care due to COPD exacerbations and comorbid complications.[7] Therefore, with the growing evidence of the impact of COPD exacerbations on patients' quality of life and incurred costs, assessing the cost-effectiveness of a COPD treatment without clinical evidence of the effect on exacerbations is a serious limitation.
- **Estimated treatment effect on COPD exacerbations:** Despite the absence of clinical evidence related to COPD exacerbations, the submitted economic model implements risk equations to estimate the number of exacerbations, with FEV_1 as one of the main predictors. Therefore, the clinical benefit of UMEC/VI versus tiotropium in terms of FEV_1 has been translated into a reduced number of exacerbations for patients on UMEC/VI treatment, resulting in estimated costs savings, a key driver of the cost difference in the submitted results. There is a great deal of uncertainty as to whether FEV_1 as a surrogate outcome and exacerbations are reliably associated, and if they are, whether the risk equation captures the association correctly. The association between FEV_1 and exacerbations has not been confirmed in the UMEC/VI clinical studies. In addition, a published study by Hurst et al.[8] identified previous exacerbations as the single best predictor of future

exacerbations. If no difference in exacerbations is assumed, the cost savings with UMEC/VI is reduced to $8 over the time horizon of 20 years.

- **Estimated treatment effect on dyspnea:** In the UMEC/VI clinical studies, there was no statistical difference between UMEC/VI and tiotropium monotherapy in terms of dyspnea. In the submitted economic model, similar to the estimate of exacerbations, FEV_1 is used as a predictor of dyspnea as well; therefore, the model results in benefits in terms of reduced dyspnea with UMEC/VI treatment, a key driver of the QALY difference in the submitted results. Assuming equal dyspnea among treatments results in an even more marginal difference in QALYs of 0.0046 (1.6 quality-adjusted days) over a time horizon of 20 years.
- **Risk equations based on ECLIPSE and TORCH data:** The ECLIPSE study was a three-year observational study, with patients primarily using a LABA/ICS regimen.[2] The TORCH study was a randomized, double-blind trial comparing the effectiveness of salmeterol (LABA), fluticasone propionate (inhaled corticosteroid [ICS]), a combination of salmeterol and fluticasone propionate (LABA/ICS), and placebo over a three-year period.[4] Based on a clinical expert opinion, the general expectation would be that patients on LABA/ICS would have more frequent exacerbations. Therefore, applying the correlations derived using these datasets to a LABA/LAMA regimen might not be appropriate.

CADTH Common Drug Review Analyses

Given the lack of evidence of treatment effect on symptom-based and patient-related end points, such as exacerbations and dyspnea, and the uncertainty regarding the correlation among the surrogate end point FEV_1 and exacerbations and dyspnea, CDR conducted a sensitivity analysis by turning off the impact of FEV_1 to these outcomes in the model. In addition, since the treatment effect of UMEC/VI on exacerbations is unknown, a scenario analysis has been conducted exploring an impact of the hypothetical difference in number of exacerbations among treatments to the incremental cost-utility ratios (ICURs).

- Excluding FEV_1 as a predictor of exacerbations and dyspnea from the risk equations resulted in a cost difference of $2 and a quality of life difference of 0.004 QALYs between UMEC/VI and tiotropium. This marginal difference in cost and QALY resulted in an ICUR of $702; i.e., the dominance of UMEC/VI over tiotropium has not been sustained any more, [redacted].
- The exploratory analysis around hypothetical difference in exacerbations among treatments confirmed the importance of this parameter to the cost-effectiveness results. Namely, assuming price parity, 5%, 10%, or 25% more exacerbations among patients on UMEC/VI versus a hypothetical comparator over the treatment period would result in an ICUR of $37,000, $98,000, or $9,000,000, respectively. Therefore, without any solid evidence of the treatment effect on exacerbations, assessing the cost-effectiveness of a COPD drug is a very difficult task.

4. ISSUES FOR CONSIDERATION

- Some of the patients who require triple therapy with LABA, LAMA, and ICS are likely to already be using a combination inhaler containing a corticosteroid plus LABA; therefore, LABA/LAMA combination inhalers such as UMEC/VI would likely not be used in this situation.
- There could be a potential for off-label use among patients with asthma.

Patient Input

COPD-related issues: Based on the received patient input, ongoing issues such as the loss of appetite, increased risk of infections, chronic bronchitis, increased reliance on supplemental oxygen, and increased risk of hospitalization and mortality are of concern for patients with COPD. With an exception of hospitalizations and mortality, none of the other raised issues has been included in the model.

Exacerbations: Patients also confirmed that exacerbations are a source of concern as they are associated with both short- and long-term effects on overall health. Although exacerbations have been modelled, the treatment effect of the exacerbations is not known.

Compliance: Based on patient input, once-daily morning treatment should help with compliance. Compliance has not been included in the economic model.

5. CONCLUSIONS

Based on the clinical trials for UMEC/VI, the results in terms of clinical outcomes for FEV_1 appear to be inconsistent when compared with tiotropium. This leads to uncertainty in the manufacturer's economic model in terms of the clinical benefit for UMEC/VI when FEV_1 is used to predict exacerbations and dyspnea. While UMEC/VI is priced [redacted] tiotropium, and less than other combination products, the clinical benefit of UMEC/VI compared with single drugs and other combination products has not been established based on the UMEC/VI clinical trials.

APPENDIX 1: COST COMPARISON TABLES

The comparators presented in the table below 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.

TABLE 3: COST COMPARISON TABLE FOR LONG-ACTING MUSCARINIC ANTAGONISTS, LONG-ACTING BETA2-AGONISTS, AND COMBINATIONS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Umeclidinium/ vilanterol (Anoro Ellipta)	**62.5 mcg/ 25 mcg**	**Inhalant pwd (30 doses)**	[redacted]	[redacted]	**62.5 mcg/ 25 mcg daily**	[redacted]	[redacted]
Other LABA/LAMA Combinations							
Indacaterol/ glycopyrronium (Ultibro	110 mcg/ 50 mcg	Inhalant pwd capsule	87.2400[b]	2.9080	110 mcg/50 mcg daily	2.91	1,061
LAMA							
Aclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd (60 doses)	53.1000[c]	0.8850	400 mcg twice daily	1.77	646
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd	1.7700	1.7700	50 mcg daily	1.77	646
Tiotropium (Spiriva)	18 mcg	Inhalant pwd	2.1667	2.1667	18 mcg daily	2.17	791
LABA							
Salmeterol (Serevent)	50 mcg	Inhalant pwd dose	0.9350	0.9400	50 mcg twice daily	1.87	683
Formoterol (Oxeze Turbuhaler)	6 mcg 12 mcg	Inhalant pwd (60 doses)	33.5280 44.6700	0.5588 0.7445	6 mcg to 12 mcg twice daily	1.12 1.49	408 543
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	0.8181	12 mcg to 24 mcg twice daily	1.64 to 3.27	597 to 1,194
Indacaterol maleate (Onbrez)	75 mcg	Inhalant pwd capsule	1.5500	1.5500	75 mcg daily	1.55	566
ICS/LABA Combinations							
Budesonide/ Formoterol (Symbicort Turbuhaler)	100 mcg/ 6 mcg 200 mcg/ 6 mcg	Inhalant pwd (120 doses)	63.7920 82.8960	0.5316 0.6908	400 mcg/12 mcg twice daily	2.76	1,009
Fluticasone furoate/Vilanterol	100 mcg/25 mcg	Inhalant pwd	130.2000[b]	4.3400	100 mcg/25 mcg once daily	4.34	1,584

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
trifenatate (Breo Ellipta)		(30 doses)					
Fluticasone propionate/ Salmeterol (Advair Diskus)	100/50 mcg 250/50 mcg 500 mcg/ 50mcg	Inhalant pwd (60 doses)	81.3900 97.4280 138.3120	1.3565 1.6238 2.3052	250/50 mcg or 500/50 mcg twice daily	3.25 to 4.61	1,186 to 1,684

CDR = CADTH Common Drug Review; ICS = inhaled corticosteroid; LABA = long-acting beta2- agonist; LAMA = long-acting muscarinic antagonist; mcg = microgram; pwd = powder.
Source: Alberta Health Drug Benefit List (September 2014) unless otherwise stated.
[a] Manufacturer's confidential submission price.
[b] McKesson Canada wholesale price (September 2014). Note that CDR recently reviewed Breo Ellipta; however, the confidential price was not made public: http://www.cadth.ca/media/cdr/complete/cdr_complete_breo_ellipta_august_20_2014.pdf.
[c] Ontario Drug Benefit Formulary (September 2014).
d

TABLE 4: COSTS OF ADDITIONAL COMPARATORS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
ICS							
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	Inhalant pwd (200 doses)	31.1600 63.7200 93.0000	0.16 0.32 0.46	200 mcg to 400 mcg twice daily	0.64 to 0.93	233 to 339
Fluticasone Propionate (Flovent Diskus, Flovent)	50 mcg 100 mcg 250 mcg 500 mcg	Inhalant pwd (60 doses)	15.1300[a] 23.9300[a] 41.2800 82.5400	0.25 0.40 0.69 1.38	100 mcg to 500 mcg twice daily	0.80 to 2.75	291 to 1,004
	50 mcg 125 mcg 250 mcg	Aerosol MDI (120 doses)	23.9300 41.2800 82.5400	0.20 0.34 0.69		0.80 to 2.75	291 to 1,004
Ciclesonide (Alvesco)	100 mcg 200 mcg	Solution aerosol (120 doses)	45.2160 74.7600	0.38 0.62	100 mcg to 800 mcg once daily	0.38 to 2.49	138 to 910
Short-acting Anticholinergic							
Ipratropium Bromide	20 mcg	MDI (200 doses)	18.9200	0.09	2 x 20 mcg 3 to 4 times daily	0.57 to 0.76	207 to 276
SABA							
Salbutamol (Airomir)	100 mcg	Inhalant pwd (200 doses)	5.0000	0.02	100 mcg to 200 mcg up to 4 times daily	0.10 to 0.20	36 to 73
Salbutamol (Ventolin, generics)	100 mcg	Inhalant pwd (200 doses)	5.0000	0.02	100 mcg to 200 mcg up to 4 times daily	0.10 to 0.20	36 to 73

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Terbutaline (Bricanyl Turbuhaler)	0.5 mg	Inhalant pwd (200 doses)	15.2800	0.08	0.5 mg up to 6 times daily	0.08 to 0.46	28 to 167
Xanthine Bronchodilator							
Theophylline (Uniphyl, generic)	100 mg 200 mg 300 mg 400 mg 600 mg	SR tab SR tab SR tab SR tab SR tab	0.1300 0.1350 0.1750 0.5030 0.6090	0.13 0.14 0.18 0.50 0.61	Once daily, generally 400 to 800 mg (varies with patient's lean muscle mass)	0.50 to 1.00	184 to 367

ICS = inhaled corticosteroid; mcg = microgram; MDI = metered-dose inhaler; mg = milligram; pwd = powder; SABA = short-acting beta2-agonist; SR = sustained release.
[a] Saskatchewan Drug Plan (September 2014).
Source: Alberta Health Formulary (September 2014) unless otherwise stated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS UMECLIDINIUM/VILANTEROL RELATIVE TO TIOTROPIUM?

UMEC/VI vs. Tiotropium[a]	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)			x			
Drug treatment costs alone						
Clinical outcomes			x[b]			
Quality of life			x[c]			
Incremental CE ratio or net benefit calculation	Uncertain, due to marginal difference in cost and QALYs[d]					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; FEV_1= forced expiratory volume in 1 second; NA = not applicable; LABA/LAMA = long-acting beta2-agonist/muscarinic antagonist; QALY = quality-adjusted life-year; SGRQ = St. George's Respiratory Questionnaire; UMEC/VI = umeclidinium/vilanterol; vs. = versus.

[a] Tiotropium is not considered to be the most appropriate comparator. The cost-effectiveness versus LABA/LAMA combination therapies remains unknown.

[b] Only one of the three tiotropium-controlled studies showed a statistically and clinical significant difference in favour of UMEC/VI in terms of trough FEV_1 as primary clinical outcome. There was no statistical difference between UMEC/VI and tiotropium monotherapy in terms of dyspnea. The effect of treatments on COPD exacerbations, major factor in COPD-related costs and quality of life has not been measured.

[c] Only one of the three tiotropium-controlled studies showed a statistically significant difference in favour of UMEC/VI in terms of SGRQ scores.

[d] CDR reviewer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			x
Comments	Major concern with a selection of comparator, as well as using the treatment benefit in terms of the surrogate end point FEV_1 as a predictor of exacerbations and dyspnea, unsupported by the available clinical evidence.		
Was the material included (content) sufficient?		x	
Was the submission well organized and was information easy to locate?		x	

FEV_1 = forced expiratory volume in one second.

TABLE 7: AUTHOR INFORMATION

Authors/Affiliations	Note
Graeme Roberts, MSc (Double Helix Consulting UK) Faisal Latif, MSc (Double Helix Consulting UK) Tam Dang-Tan, PhD (Double Helix Consulting UK) Shiyuan (William) Zhang, MSc (GlaxoSmithKline Canada) Emma Goodall, PhD (GlaxoSmithKline Canada)	The COPD Progression Model has been developed by Oxford Outcomes, and further adopted for UMEC/VI for Canada by Double Helix Consulting UK for GlaxoSmithKline Canada

	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

COPD = chronic obstructive pulmonary disease; GSK = GlaxoSmithKline; UK = United Kingdom; MSc = Masters of Science; PhD = Doctor of Philosophy; UMEC/VI = umeclidinium/vilanterol.

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS

TABLE 8: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	Scottish Medicines Consortium (July 2014)[7]
Treatment	UMEC/VI
Price	£394 per year (C$710)
Similarities with CDR submission	Same model structure, same data inputs
Differences with CDR submission	In addition to tiotropium as a comparator, it was also compared with indacaterol plus tiotropium.
Manufacturer's results	UMEC/VI dominates tiotropium and indacaterol/tiotropium
Issues noted by the review group	• The comparison with tiotropium alone was deemed inappropriate. The only direct comparative evidence is against tiotropium monotherapy, which is not considered as a relevant comparator to dual LABA/LAMA therapy. Despite the expectation that dual therapy with umeclidinium/vilanterol would be superior to tiotropium monotherapy, the differences were not always significant in terms of the important patient-related outcomes (reduced breathlessness, use of rescue medication, and improved quality of life). It is unclear how the efficacy of the umeclidinium/vilanterol combination inhaler compares to existing LABA/LAMA therapy. • The evidence driving the analysis versus separate inhalers of indacaterol and tiotropium was the FEV_1 results from the indirect comparison. As noted in the clinical effectiveness section, there were weaknesses with this analysis that limit the validity of the conclusions from the analysis. In addition, this indirect comparison showed that the treatment difference was not statistically significant, yet the numerical advantages were used to drive the results of the model. • A complex modelling structure using risk equations was used; however, the results indicated that the resulting QALY gains were very small and the overall cost difference was driven overwhelmingly by drug costs only (£2,831 of the overall difference in costs of £2,834). It could have been argued that a simpler analytical approach such as a cost-minimization analysis could have been adopted for this comparison.
Results of reanalyses by the review group (if any)	None
Recommendation	Do not list

C$ = Canadian dollars; CDR = CADTH Common Drug Review; FEV_1 = forced expiratory volume in one second; LABA = long-acting beta2-agonists; LAMA = long-acting muscarinic antagonist; QALY = quality-adjusted life-year; UMEC/VI = umeclidinium/vilanterol.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a chronic obstructive pulmonary disease (COPD) progression risk equation model with a 20-year time horizon and cycle length of one year, comparing umeclidinium bromide/vilanterol trifenatate (UMEC/VI) with tiotropium.

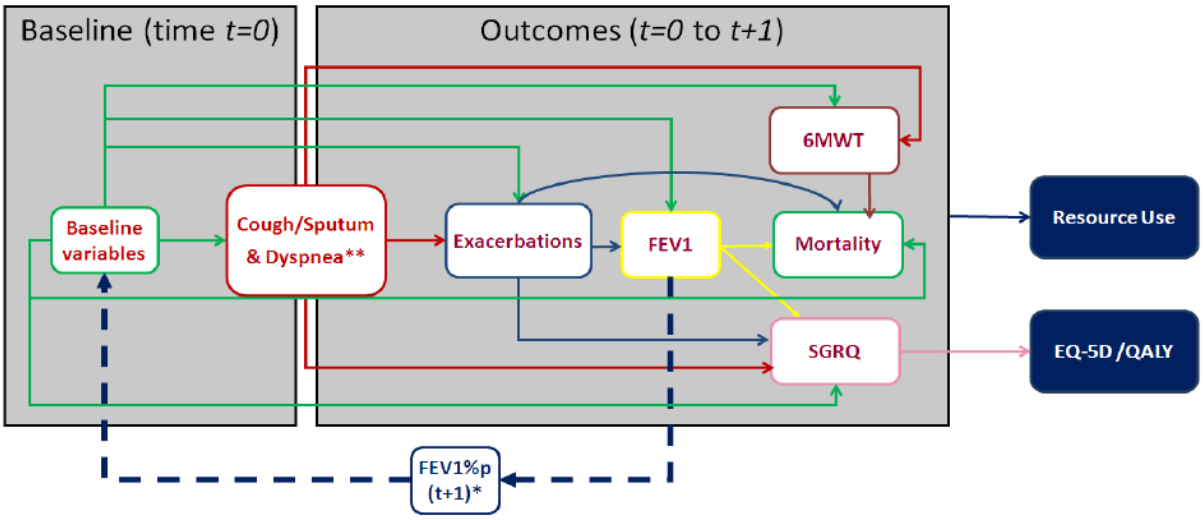
Patients moved through the model based on statistical risk equations that correlate patient characteristics — age, sex, body mass index, comorbidities, prior exacerbation history, presence of symptoms, smoking status, fibrinogen biomarkers, St. George's Respiratory Questionnaire (SGRQ) health status, lung function, and exercise capacity — the primary outcome (per cent predicted forced expiratory volume in one second [FEV_1]), the intermediate model outcomes (exacerbations, cough and sputum, and six-minute walk test), and the final model outcomes (costs, mortality, and quality of life) (Figure 1). As such, there are risk equations for each of the following:

- dyspnea proportion with symptoms most days per week
- dyspnea proportion with no symptoms each week
- cough and sputum proportion with symptoms most days per week
- moderate exacerbation count per patient per year
- severe exacerbation count per patient per year
- FEV_1 in millilitres, then converted to FEV_1% predicted
- six-minute walk test distance in metres per year
- SGRQ-C (for COPD) Score
- survival.

The statistical risk equations for clinical end points were derived from analysis using data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate (ECLIPSE) study,[2] and the TOwards a Revolution in COPD Health (TORCH) study[4] for resource use. The clinical parameters were used to estimate SGRQ scores, which were mapped into EuroQol 5-Dimensions Questionnaire (EQ-5D) based on a published algorithm.[3] The unit costs were based on Canadian sources.

The submitted model schematic is presented in **FIGURE** 1. The model is initiated by first running the dyspnea and cough and sputum risk equations to predict the risk equation outputs at baseline. As a next step, the predicted baseline values for the dyspnea, cough and sputum risk equations, and the observed baseline per cent predicted FEV_1 values are used to estimate the exacerbation counts. The six-minute walk test and SGRQ are predicted using the baseline per cent predicted FEV_1 and the exacerbations outputs, along with the baseline predicted dyspnea and cough and sputum outputs. Survival is predicted each year based on the survival risk equation, which included the cumulative exacerbations in the past 12 months, per cent predicted FEV_1, dyspnea, cough and sputum as well as the baseline demographic parameters. Resource utilization counts are estimated each year based on the cumulative exacerbation counts during the same year, current per cent predicted FEV_1 and current level of dyspnea and cough and sputum symptoms.

FIGURE 1: MANUFACTURER'S SUBMITTED RISK EQUATION MODEL SCHEMATIC



*Note FEV1% at baseline assumed to be FEV1% lagged for the first symptom estimation; FEV1 converted to FEV1% predicted for beginning on next mode iteration

**Note Cough/Sputum & Dyspnea are predicted at baseline and as outcomes at t+1

Source: Manufacturer's Pharmacoeconomic Submission[5]
6MWT = six-minute walk test; EQ-5D = EuroQoL 5-Dimensions; FEV_1 = forced expiratory volume in one second; QALY = quality-adjusted life-year; SGRQ = St. George's Respiratory Questionnaire.

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	The efficacy input used in the economic model is LS mean difference for trough FEV_1 at 24 weeks. It is derived from unpublished meta-analysis from the pivotal studies that included the tiotropium group (DB2113374, DB2113360, and ZEP117115).	The lung function captured through FEV_1 difference is the only data input in the model that differentiates the two treatments. Therefore, any uncertainty regarding this estimate has principal impact to the model. The absence of efficacy input in terms of exacerbation count is a major limitation.
Natural history	Natural history of disease has been estimated based on statistical risk equations derived from analysis using data from the ECLIPSE study, adjusted with baseline characteristics.	ECLIPSE study was a 3-year observational study, with patients primarily using a LABA/ICS regimen. Therefore, the correlations derived might not be appropriate for LABA/LAMA regimen, as the general expectation would be that patients on LABA/ICS would have more frequent exacerbations.
Baseline characteristics	The baseline characteristics are derived from UMEC/VI trials where available. For the inputs unavailable from the trials, such as fibrinogen, % of severe exacerbations, and 6-minute walk distance, default values from ECLIPSE study	The difference in patient characteristics in ECLIPSE study and the UMEC/VI trials might bias the results. A subgroup of ECLIPSE patients to match the UMEC/VI patient population would have been more

Data Input	Description of Data Source	Comment
	were used.	appropriate.
Utilities	The clinical parameters in the model were used to estimate SGRQ scores, which were further mapped into EQ-5D based on a published algorithm by Starkie.[3]	Statistically significant difference in quality of life measured in terms of SGRQ was not achieved in 2 out of 3 trials comparing UMEC/VI with tiotropium. The mapping algorithm that was used is published and validated, but needs to be used with caution. The author of the study concluded that for use within an HTA submission (in which precision of estimation is important), it is in both the interests of the manufacturer and the HTA body that utility scores are directly derived from the clinical trial population.[3]
Resource use	Estimated based on statistical risk equations derived from analysis using data from the TORCH study.	It is known that resource use in a clinical trial setting and a real-life setting has substantial differences; however, the nature of the model does not allow a more detailed review of resource use in order to be assessed. In addition, the difference in patient characteristics in TORCH study and the UMEC/VI trials might bias the results.
Adverse events	Not included	Per CDR clinical report, incidence of overall AEs was generally similar across treatment groups in each study.
Mortality	The mortality has been estimated based on statistical risk equations using ECLIPSE study data, which included the cumulative exacerbations in the past 12 months, FEV_1% predicted, dyspnea, cough and sputum as well as the baseline demographic parameters.	The fact that the number of exacerbations is the main predictor of mortality, and there is no evidence of the difference among treatments in terms of exacerbations, is a serious issue and results in uncertainty around the estimates. In addition, similar to the other risk equations, the difference among the patient populations in ECLIPSE vs. UMEC/VI trials might bias the results.
Costs		
Drug costs	Drug cost of tiotropium is based on Ontario Drug Benefit Formulary and is being applied for one year, since the model assumes a 1-year treatment duration.	Prescription fee costs and mark-up have not been included.
- Event	The costing methodology for the resource utilization counts (hospital days, ER visits, and physician contact visits) is based on statistical risk equations based on TORCH study. For each year of the model, the predicted resource utilization counts are multiplied by Canadian	The cost for moderate and severe exacerbations are based on 2008 Canadian study by Mittman et al.,[9] and they seem appropriate. The costs by dyspnea symptoms status are derived from a previous HE model by Spencer et al.[10]

Data Input	Description of Data Source	Comment
	specific unit costs for moderate and severe exacerbations and health state costs by dyspnea symptom status, derived from Canadian published literature.	(2005).

AEs = adverse events; CDR = CADTH Common Drug Review; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate; EQ-5D = EuroQol 5-Dimensions Questionnaire; ER = emergency room; FEV_1 = forced expiratory volume in one second; HE = health economic; HTA = Health Technology Assessment; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonists; LAMA = long-acting muscarinic antagonist; LS = least squares; SGRQ = St. George's Respiratory Questionnaire; TORCH = TOwards a Revolution in COPD Health; UMEC/VI = umeclidinium/vilanterol; vs. = versus.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Disease progression and resource use estimates are representative of the cohort selected, and the ECLIPSE and TORCH data are generalizable to the UMEC/VI patient population.	ECLIPSE study was a 3-year observational study, with patients primarily using a LABA/ICS regimen.[2] TORCH study was a randomized, double-blind trial comparing the effectiveness of salmeterol, fluticasone propionate, a combination of salmeterol and fluticasone propionate, and placebo over a 3-year period.[4] Therefore, the correlations derived using these datasets might not be appropriate for a LABA/LAMA regimen, as the general expectation would be that patients on LABA/ICS would have more frequent exacerbations.
Treatment duration and treatment benefit are assumed to be 1 year.	If the aim of the model is to show the effect on FEV_1, then this might be appropriate, as per clinical expert opinion. However, looking at the exacerbation and hospital visits, this might be too a short period, as the patients with prior exacerbations are very likely to have another one.
For the baseline prediction of the proportion estimates for the dyspnea and cough and/or sputum equations, the lagged value for per cent predicted FEV_1 (i.e., a year before baseline) is not known; therefore, it is assumed the per cent predicted FEV_1 at baseline was the lagged per cent predicted FEV_1.	Appropriate modelling assumption.

ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonists; LAMA = long-acting muscarinic antagonist; TORCH = TOwards a Revolution in COPD Health; UMEC/VI = umeclidinium/vilanterol.

Manufacturer's Results

In the reference case, the manufacturer reported that the total cost for UMEC/VI was $30,956, a reduced cost of $153 compared with tiotropium ($31,108). Patients using UMEC/VI treatment experienced an average of 1.145 exacerbations per year — a decrease of 0.009 in comparison with tiotropium (1.154). Treatment with UMEC/VI resulted in 4.37 total quality-adjusted life-years (QALYs), an additional 0.01 QALY compared with tiotropium (4.36). Hence, the manufacturer reported that UMEC/VI dominates tiotropium (more effective, less expensive).

TABLE 11: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of UMEC/VI ($)	Total QALYs	Incremental QALYs of UMEC/VI	Incremental Cost per QALY
UMEC/VI	30,956	–$153	4.37	0.01	dominant
Tiotropium	31,108		4.36		

QALYs = quality-adjusted life-years; UMEC/VI = umeclidinium/vilanterol
Source: Manufacturer's pharmacoeconomic submission.[5]

The following table presents the results summary of the cost-effectiveness of UMEC/VI versus tiotropium based on the submitted economic model.

TABLE 12: RESULTS SUMMARY OF THE COST-EFFECTIVENESS OF UMECLIDINIUM/VILANTEROL VERSUS TIOTROPIUM

	UMEC/VI	Tiotropium
Cumulative Number of Exacerbations Over Timeframe		
Moderate	5.90	5.96
Severe	4.55	4.57
Total	10.45	10.53
Average exacerbations per year	1.145	1.154
Outcomes at End of Timeframe		
Survival at end of time horizon	0.0%	0.0%
Accumulated life-years (undiscounted)	8.88	8.88
Accumulated QALYs	4.37	4.36
Costs at End of Timeframe		
Accumulated costs total	$30,956	$31,108
Drug costs	[redacted]	[redacted]
Non-drug costs (costs of exacerbations, dyspnea)	[redacted]	[redacted]

QALYs = quality-adjusted life-years.
Source: Taken in part from manufacturer's pharmacoeconomic submission.[5]

Deterministic One-Way Sensitivity Analysis

The manufacturer reported that based on its deterministic one-way sensitivity analyses, treatment costs of UMEC/VI and tiotropium are the parameters that have the greatest impact on outcomes.
A sensitivity analysis showed that only treatment effects on l FEV_1 had an impact on the results, and this was minimal.

Based on the submitted sensitivity analysis, UMEC/VI was dominant over tiotropium in all cases.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analyses (PSAs) were run in three scenarios, all with a treatment duration and effect of one year, but varying the model time horizon to 1 year, 5 years, and 10 years. In all scenarios and in the majority of cases, UMEC/VI was dominant (incrementally less costly and more effective) over tiotropium. In 81.3% of the simulations, UMEC/VI was dominant over tiotropium, and in 18.7% of the simulations, it was incrementally less costly but also less effective than tiotropium.

CADTH Common Drug Review Reanalysis

Given the uncertainty regarding the correlation among FEV_1 and exacerbations and dyspnea, CADTH Common Drug Review (CDR) considered a conservative analysis, and conducted sensitivity analysis by switching off the impact of FEV_1 to these outcomes. In addition, since the treatment effect of UMEC/VI to exacerbation is unknown, a scenario analysis has been conducted exploring the impact of the hypothetical difference in number of exacerbations among treatments to the incremental cost-utility ratios (ICURs).

Reanalyses Removing the Impact of FEV_1 on Exacerbations and Dyspnea Risk Equations

The results of these analyses show that [redacted] of UMEC/VI and tiotropium, the dominance of UMEC/VI over tiotropium has been achieved by estimated savings with UMEC/VI treatment due to fewer severe exacerbations. Namely, when the impact of FEV_1 on exacerbations is switched off, the difference in cost is lowered to a marginal $8 over 25 years.

The more favorable results in terms of QALYs have been achieved mostly due to improvement of symptoms and dyspnea. Switching off the impact results in a difference in QALY of 0.005.

Combining these two analyses resulted in a $2 difference in costs and a 0.004 difference in QALY (1.2 quality-adjusted days) (Table 13).

TABLE 13: REANALYSES REMOVING THE IMPACT OF FORCED EXPIRATORY VOLUME IN ONE SECOND ON EXACERBATIONS AND DYSPNEA RISK EQUATIONS

UMEC/VI vs. Tiotropium	Difference in QALYs	Difference in Life-Years	Difference in Costs	ICUR
Default	0.014	0.003	–$153	UMEC/VI dominant
No impact on moderate exacerbations	0.014	0.003	–$137	UMEC/VI dominant
No impact on severe exacerbations	0.014	0.003	–$24	UMEC/VI dominant
No impact on moderate and severe exacerbations	0.013	0.003	–$8	UMEC/VI dominant
No impact on dyspnea, level 2	0.014	0.003	–$152	UMEC/VI dominant
No impact on dyspnea, level 3	0.005	0.002	–$150	UMEC/VI dominant
No impact on dyspnea level 2 and 3	0.005	0.002	–$150	UMEC/VI dominant
No impact on dyspnea nor exacerbations	0.004	0.002	$2[a]	$708

ICUR = incremental cost-utility ratio; QALYs = quality-adjusted life-years; UMEC/VI = umeclidinium/vilanterol; vs. = versus.
[a] This result is due to the small survival gain with UMEC/VI.

Scenario Analyses Exploring the Impact of Exacerbations

In order to show the significant impact of exacerbations on the ICURs, an exploratory analysis has been conducted by exploring a hypothetical difference in number of severe exacerbations at year 1. For this analysis, the impact of FEV_1 on exacerbations has been switched off, as in the previous analyses, and imputed values have been used in the model. These analyses need to be used with caution, since the structure of the model does not capture the impact of the exacerbations on quality of life, and it estimates only the impact of exacerbations on cost. If the impact of exacerbations on quality of life has been captured, it is expected that UMEC/VI would be dominated (Table 14).

TABLE 14: SCENARIO ANALYSIS EXPLORING THE IMPACT OF EXACERBATIONS

UMEC/VI vs. Hypothetical Comparator	Difference in QALYs	Difference in Life-Years	Difference in Costs	ICUR
5% increase in severe exacerbations during treatment effect with UMEC/VI	0.003	0.002	$107	$37,648
10% increase in severe exacerbations during treatment effect with UMEC/VI	0.002	0.002	$211	$98,517
25% increase in severe exacerbations during treatment effect with UMEC/VI	0.000	0.002	$523	$9,296,852

ICUR = incremental cost-utility ratio; QALYs = quality-adjusted life-years; UMEC/VI = umeclidinium/vilanterol; vs. = versus.

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