Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	fluticasone furoate/vilanterol (Breo Ellipta)
Indication	BREO ELLIPTA (fluticasone furoate/vilanterol) is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations.
Listing request	For the maintenance treatment of moderate to severe COPD, to reduce exacerbations.
Manufacturer	GlaxoSmithKline Canada

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 CADTH 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

BUD	budesonide
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
DPI	dry powder inhaler
FEV_1	forced expiratory volume in one second
FF	fluticasone furoate
FM	formoterol
FP	fluticasone propionate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
LAAC	long-acting anticholinergic
LABA	long-acting beta2-agonist
SAAC	short-acting anticholinergic
SABA	short-acting beta2-agonist
SAL	salmeterol
V	vilanterol

SUMMARY

Fluticasone furoate/vilanterol (FF/V) 100/25 mcg is the combination product of an inhaled corticosteroid (ICS) and long-acting beta2-agonist (LABA), available as a dry powder inhaler for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for reducing exacerbations of COPD in patients with a history of exacerbations. The confidential price per 30-actuation inhaler is [redacted] or [redacted] per day.

The manufacturer submitted a cost-minimization analysis comparing FF/V to fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg and 500/50 mcg in adult patients with moderate to severe COPD, with forced expiratory volume in one second (FEV_1) ≤ 70% predicted post-bronchodilator, over a five-year time horizon. Equivalent efficacy and safety was assumed between treatments based on head-to-head clinical trials of FF/V. [redacted] CADTH Common Drug Review calculations confirmed that FF/V is less expensive than FP/SAL (250/50 mcg to 500/50 mcg twice daily, $3.25 to $4.61 daily). FF/V is [redacted] budesonide/formoterol (400/12 mcg twice daily, $2.76 daily), but more expensive than the three long-acting anticholinergics available in Canada ($1.77 to $2.35 daily), which were not considered as comparators by the manufacturer. FF/V is also more expensive than combination therapy with budesonide and formoterol administered separately ($2.41 to $2.57 daily).

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Breo Ellipta (fluticasone furoate/vilanterol; FF/V) is a combination product comprising an inhaled corticosteroid (ICS) and a long-acting beta2-adrenergic agonist (LABA) that is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. FF/V is available as a 100/25 mcg powder for inhalation in an inhaler containing 30 actuations at a confidential price of [redacted] ([redacted] per day at the recommended dose of 100/25 mcg once daily). FF and vilanterol (V) are not currently available as individual agents.

1.1 Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. 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 1: COST COMPARISON TABLE FOR ICS/LABAS AND LAACS FOR COPD

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Fluticasone furoate/vilanterol trifenatate (Breo Ellipta)	**100/25 mcg**	**Inhalant pwd (30 doses)**	[redacted][a]	[redacted]	**100/25 mcg once daily**	[redacted]	[redacted]
ICS/LABA Combinations							
Budesonide/ formoterol (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	Inhalant pwd (120 doses)	63.7920 82.8960	0.5316 0.6908	400/12 mcg twice daily	2.76	1,009
Fluticasone propionate/ Salmeterol (Advair DISKUS)	100/50 mcg 250/50 mcg 500/50 mcg	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
Individual Components of ICS/LABA Combinations							
Fluticasone propionate (Flovent DISKUS, Flovent)	50 mcg 100 mcg 250 mcg 500 mcg	Inhalant pwd (60 doses)	15.1300[b] 23.9300[b] 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			
Salmeterol (Serevent)	50 mcg	Inhalant pwd dose	0.9350	0.94	50 mcg twice daily	1.87	683
Budesonide (Pulmicort	100 mcg 200 mcg	Inhalant pwd	31.1600 63.7200	0.16 0.32	200 mcg to 400 mcg	0.64 to 0.93	233 to 339

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Turbuhaler)	400 mcg	(200 doses)	93.0000	0.46	twice daily		
Formoterol (Oxeze Turbuhaler)	6 mcg 12 mcg	Inhalant pwd (60 doses)	33.5280 44.6700	0.56 0.74	6 mcg to 12 mcg twice daily	1.12 1.49	408 543
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	0.82	12 mcg to 24 mcg twice daily	1.64 to 3.27	597 to 1,194
LAACs							
Aclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd (60 doses)	70.5300[c]	1.1755	400 mcg twice daily	2.35	859
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.7700	50 mcg daily	1.77	646
Tiotropium (Spiriva)	18 mcg	Inhalant pwd capsule	2.1667	2.1667	18 mcg daily	2.17	791

ICS = inhaled corticosteroid; LAAC = long-acting anticholinergic; LABA = long-acting beta2-agonist; pwd = powder.
[a] Manufacturer's confidential submission price.
[b] Saskatchewan Drug Plan (April 2014).
[c] McKesson Canada wholesale price (April 2014).
Source: Alberta Health Drug Benefit List (April 2014) unless otherwise stated.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted cost-minimization analyses with the perspective of a "public pharmaceutical payer" with a time horizon of five years. Costs were discounted 5% and were obtained from the Alberta Ministry of Health, as Alberta lists all comparators of interest as full benefits. The analyses compared FF/V to fluticasone propionate/salmeterol (FP/SAL), another ICS/LABA combination product, at twice-daily 250/50 mcg or 500/50 mcg doses. The target population consisted of adults with moderate to severe COPD, with $FEV_1 \leq 70\%$ predicted post-bronchodilator.

While the manufacturer submitted a cost-minimization analysis,[1] the analyses were based on an initial decision tree followed by a five-year Markov model. The model consisted of FEV_1-based health states, each with and without recent exacerbations: less than 30% predicted, 30% to less than 50% predicted, 50% to less than 70% predicted, and death. Mortality over the five-year analysis period was based on Canadian general population life tables, and applied similarly to treatment, based on patient characteristics from the TORCH and UPLIFT trials. The use of a cost-minimization analysis is based on the assumption of comparable efficacy and safety between FF/V and both strengths of FP/SAL based on the results of three clinical trials.[2-4] As such, the model was used to calculate the difference in drug treatment costs, as other costs (cost of treating exacerbations, pneumonia, etc.) were identical across treatment groups.

In the manufacturer's base case, the five-year discounted cost of FF/V ([redacted]) when compared with FP/SAL 250/50 ([redacted]) was [redacted] less expensive. When compared with FP/SAL 500/50 ([redacted]), the manufacturer estimated the five-year discounted cost of FF/V ([redacted]) was [redacted] less expensive. The difference in the cost of FF/V between analyses is due to slight differences in population characteristics affecting mortality (e.g., time on treatment). The estimated five-year treatment costs are significantly less than five times the annual drug cost (Table 1) because of the incorporation of mortality probability into the results as well as discounting.

3. KEY LIMITATIONS

Appropriate Comparators Were Omitted

The manufacturer acknowledged that budesonide (BUD)/ formoterol (FM), the other available ICS/LABA combination product, would ideally have been incorporated into its economic analysis. A claims analysis[5] indicating that FP/SAL was the most commonly used ICS/LABA combination for treating COPD, as well as an absence of clinical trials comparing BUD/FM with either FF/V or FP/SAL, were the basis of the manufacturer's selection of FP/SAL as the comparator. Since the manufacturer's submission, one network meta-analysis sponsored by the manufacturer and presented as a poster[6] concluded that FF/V 92/22 mcg daily demonstrated similar efficacy on lung function to FP/SAL 500/50 mcg and BUD/FM 400/12 mcg twice daily, but there was insufficient data to adequately compare exacerbation rates. Another network meta-analysis[7] concluded that COPD exacerbation prevention with ICS/LABA combination agents was a class effect, with no particular formulation showing an advantage over the others, including both FF/V and BUD/FM.

Also, according to the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[8] and the 2007 Canadian Thoracic Society (CTS) guidelines,[9] long-acting anticholinergics (LAACs) are another treatment option for moderate to severe COPD. While FF/V is less expensive than FP/SAL and [redacted] BUD/FM, it is more expensive than all three of the LAACs currently available in Canada. The cost-effectiveness of FF/V relative to LAAC agents is unknown, although one 12-week trial of patients with COPD and comorbid cardiovascular disease did not find a statistically significant or clinically meaningful difference in efficacy between FF/V and tiotropium.[10] See APPENDIX 2 for price-reduction scenarios setting the price of FF/V to be equivalent to the price of LAACs. See also Issues for Consideration, Triple Therapy.

Assumption of Clinical Equivalence

The manufacturer provided direct evidence to show that FF/V is likely comparable, at least in the short term, to FP/SAL. It is uncertain whether this equivalence would continue over a longer time period. While it can be useful to model differences in treatments over a longer time span than is practical in clinical trials to determine the consequences of each treatment, with equivalent transition probabilities and utilities assumed between comparators, this exercise provides little value. In any case, it remains uncertain that treatment similarities or differences perceived in 12-week trials would persist over five years.

While BUD/FM was not included in the manufacturer's analyses, the submitted price of FF/V [redacted] BUD/FM if an assumption of clinical equivalence is made. This assumption appears to be supported by two recent network meta-analyses, albeit of varying doses of FF/V.[6,7]

Individual Agents Not Available

Neither fluticasone furoate nor vilanterol trifenate are available individually in Canada. Physicians will not have the option of starting or stopping patients on the individual components prior to combination use, an issue that is complicated by the variation in coverage for LABA products. For example, FP/SAL, BUD/FM, and FM alone are covered for asthma but not COPD by the Ontario Drug Benefit Formulary and the Non-Insured Health Benefits program, while SAL is reimbursed for COPD only if a patient fails to respond to a short-acting beta2-agonist (SABA) *and* a LAAC. In contrast, Saskatchewan will reimburse SAL or FM if the patient has been unresponsive to a SABA *or* short-acting anticholinergic (SAAC) and will reimburse FP/SAL or BUD/FM if the patient is using or has used a LABA or LAAC. The absence of V as an individual agent may make the FF/V combination less desirable to clinicians who are adding on to previous therapies and working within limited use criteria.

The FP/SAL combination inhalers are less expensive than their individual components; however, BUD and FM administered separately are less expensive than the combination BUD/FM inhaler [redacted] FF/V. See APPENDIX 2, Table 5.

Complexity of Model

The manufacturer submitted a complex model incorporating mortality, exacerbations, and pneumonia. With the assumption of clinical equivalence, these variables do not assist in determining the cost-effectiveness of FF/V compared with FP/SAL (see Assumption of Clinical Equivalence, section 3). Estimations of patient mortality over five years may assist in budget-impact analyses; however, they are of limited value in a cost-minimization analysis and may lead to misunderstandings and subsequent underestimation of the cost differences between comparators over five years.

Markups Not Considered

The manufacturer's analyses used Alberta Health–listed drug costs and a $10 dispensing fee four times annually without accounting for markups. The current allowable Alberta markups total 8.665%, with a pharmacy fee of $12.30. Given the 30-day supply inherent in ICS/LABA inhalers, it is probable that the pharmacy fee will be applied in practice at least every 90 days. While these differences do not affect the direction of relative costs, they do enhance the absolute differences, making FF/V less expensive than the manufacturer estimated relative to ICS/LABA comparators, but more expensive relative to LAACs than would have been estimated had the manufacturer included them in the analyses (see Table 2).

TABLE 2: ANNUAL AND RELATIVE COSTS OF COMPARATORS USING MANUFACTURER'S ESTIMATE METHOD AND ALBERTA HEALTH RATES

Comparator	Drug Cost + 0% Markup and $10 Fee Four Times Annually[a]		Drug Cost + 8.665% Markup and $12.30 Fee Every 90 Days[a]	
	Annual Cost	Relative Annual Cost	Annual Cost	Relative Annual Cost
Fluticasone propionate + salmeterol (Flovent 500 + Serevent)[a]	$1,767	[redacted]	$1,934	[redacted]
Fluticasone propionate/ salmeterol (Advair DISKUS 500/50)	$1,724	[redacted]	$1,880	[redacted]
Fluticasone propionate + salmeterol (Flovent 250 + Serevent)[a]	$1,266	[redacted]	$1,388	[redacted]

Comparator	Drug Cost + 0% Markup and $10 Fee Four Times Annually[a]		Drug Cost + 8.665% Markup and $12.30 Fee Every 90 Days[a]	
	Annual Cost	Relative Annual Cost	Annual Cost	Relative Annual Cost
Fluticasone propionate/ salmeterol (Advair DISKUS 250/50)	$1,226	[redacted]	$1,339	[redacted]
Budesonide/formoterol (Symbicort Turbuhaler)	$1,049	[redacted]	$1,147	[redacted]
Fluticasone furoate/vilanterol trifenatate (Breo Ellipta)	[redacted]	**Reference**	[redacted]	**Reference**
Aclidinium bromide (Tudorza Genuair)	$899	[redacted]	$983	[redacted]
Tiotropium (Spiriva)	$831	[redacted]	$910	[redacted]
Budesonide + formoterol (Pulmicort + Oxeze)[a]	$718	[redacted]	$794	[redacted]
Glycopyrronium bromide (Seebri)	$686	[redacted]	$752	[redacted]

[a] Fee applies to both products for combination therapy with individual drugs.

4. ISSUES FOR CONSIDERATION

Patient Convenience and Adherence

While there are little data to support the benefit of once-daily dosing over twice daily for COPD medications, it is possible that patients will value or benefit from a decreased dosing schedule. Additionally, the novel dry powder inhaler (DPI) mechanism may be easier to use, which could reduce DPI handling error rates, a considerable problem in COPD.[11]

Triple Therapy

According to the 2014 GOLD guidelines and the 2007 CTS guidelines, it may be appropriate for some patients with many symptoms who are at high risk of exacerbations (i.e., Group D patients within the GOLD guidance and patients with severe impairment in that of the CTS guidelines) to receive triple therapy with an ICS, a LABA, and a LAAC.[8] Costs for such patients will be higher than those on ICS/LABA alone, but using FF/V as part of a triple-therapy regime [redacted] its current comparators. However, combination LABA/LAAC products have recently received Health Canada approval. Depending on the pricing of these new products and which options are recommended or regularly prescribed as part of a triple-therapy regimen, FF/V may not be one of the lower-cost component options for patients requiring ICS, LABA, and LAAC therapy.

5. CONCLUSIONS

At the submitted confidential price of [redacted] per 100/25 mcg inhaler ([redacted] daily), compared with other ICS/LABA combinations already reimbursed in some jurisdictions for the treatment of COPD, FF/V is less expensive than FP/SAL (250/50 to 500/50 mcg twice daily, $3.25 to $4.61 daily) and [redacted] BUD/FM (400/12 mcg twice daily, $2.76 daily). If listed, and assuming equivalent efficacy and safety assumptions are valid, FF/V would not result in additional costs for patients who would otherwise be prescribed an ICS/LABA combination, but is more expensive than monotherapy with the available LAACs ($1.77 to $2.35 daily), another recommended treatment option for patients with more moderate COPD. For the cost of FF/V to be equivalent to LAAC products, the price of FF/V would need to be reduced by [redacted] %.

APPENDIX 1: ADDITIONAL COMPARATOR COSTS

TABLE 3: 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 ($)	Annual Drug Cost ($)
Long-Acting Beta2-Agonist							
Formoterol (Oxeze Turbuhaler)	6 mcg 12 mcg	Inhalant pwd (60 doses)	33.5280 44.6700	0.56 0.74	6 mcg to 12 mcg twice daily	1.12 1.49	408 543
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	0.82	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	1.55	75 mcg daily	1.55	566
Salmeterol (Serevent)	50 mcg	Inhalant pwd dose	0.9350	0.94	50 mcg twice daily	1.87	683
ICSs							
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 (Atrovent)	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
Short-Acting Beta2-Agonist							
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
Terbutaline (Bricanyl Turbohaler)	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

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Drug Cost ($)
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; MDI = metered dose inhaler; pwd = powder; SR tab = slow-release tablet.
[a] Saskatchewan Drug Plan (April 2014).
Source: Alberta Health Formulary (April 2014) unless otherwise stated.

APPENDIX 2: PRICE-REDUCTION SCENARIOS

Because FF/V is more expensive than the available LAACs for the treatment of COPD, CDR calculated the price reduction required for FF/V to equal the cost of each available LAAC. Additionally, while FF/V is [redacted] BUD/FM combination product, it is more expensive than BUD and FM administered separately.

TABLE 4: CADTH COMMON DRUG REVIEW ANALYSIS FOR PRICE-REDUCTION SCENARIOS FOR FF/V BASED ON THE PRICE OF AVAILABLE LAACS

Current Price Per FF/V Inhaler	Current Cost Per Day	Scenario	Reduction Needed (%)	Reduced Cost Per Day	Reduced Price Per FF/V Inhaler
[redacted]	[redacted]	Price reduction needed to equal aclidinium (Tudorza Genuair)	[redacted]	$2.35	$70.53
		Price reduction needed to equal tiotropium (Spiriva)	[redacted]	$2.17	$65.00
		Price reduction needed to equal glycopyrronium (Seebri)	[redacted]	$1.77	$53.10

FF/V = fluticasone furoate/vilanterol; LAAC = long-acting anticholinergic.

Note: Prices are from the Alberta Health Formulary with the exception of Tudorza Genuair, which is the McKesson Canada wholesale price.

TABLE 5: CADTH COMMON DRUG REVIEW ANALYSIS FOR PRICE-REDUCTION SCENARIOS FOR FF/V BASED ON THE PRICES OF BUD AND FM PRODUCTS

Current Price Per FF/V Inhaler	Current Cost Per Day	Scenario	Reduction Needed (%)	Reduced Cost Per Day	Reduced Price Per FF/V Inhaler
[redacted]	[redacted]	Price reduction needed to equal BUD/FM (Symbicort)	[redacted][a]	[redacted]	[redacted]
		Price reduction needed to equal BUD + FM (Pulmicort + Foradil)	[redacted]	$2.57	$77.10
		Price reduction needed to equal BUD + FM (Pulmicort + Oxeze)	[redacted]	$2.41	$72.30

BUD = budesonide; FF/V = fluticasone furoate/vilanterol; FM = formoterol.

Note: Prices are from the Alberta Health Formulary. Note that while pharmacy dispensing fees and markups are not included in these calculations, the additional fee applicable to a second prescription product (approximately $0.137 per day in Alberta for a 90-day supply) should be considered when comparing the costs of individual components to combination inhalers.

[a] At the confidential price, FF/V is [redacted] BUD/FM (Symbicort).

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