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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

FLUTICASONE PROPIONATE (AERMONY RESPICLICK — TEVA CANADA INNOVATION)
Indication: Maintenance treatment of asthma in patients 12 years of age and older.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that fluticasone propionate multi-dose dry powder inhaler be reimbursed for the maintenance treatment of steroid-responsive bronchial asthma as a prophylactic therapy in patients 12 years of age and older, if the following condition is met:

Condition
Fluticasone propionate multi-dose dry powder inhaler should provide cost savings for drug plans relative to the lowest priced alternative inhaled corticosteroid reimbursed for the treatment of asthma.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	Final
Publication Date:	December 21, 2018
Report Length:	8 Pages

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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

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

FLUTICASONE PROPIONATE (AERMONY RESPICLICK — TEVA CANADA INNOVATION)

Indication: Maintenance treatment of asthma in patients 12 years of age and older.

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone propionate multi-dose dry powder inhaler (Fp MDPI) be reimbursed for the maintenance treatment of steroid-responsive bronchial asthma as a prophylactic therapy in patients 12 years of age and older, if the following condition is met:

Condition

- Fp MDPI should provide cost savings for drug plans relative to the lowest priced alternative inhaled corticosteroid (ICS) reimbursed for the treatment of asthma.

Reasons for the Recommendation

1. In one phase I, multicenter, open-label, randomized, active-controlled, four-period crossover, single-dose study (Study 10042 [N = 40]), Fp MDPI was associated with systemic exposure of Fp that was approximately 20% to 30% lower than with Fp dry powder inhaler (DPI; Flovent Diskus).
2. In two phase II, randomized, double-blind placebo- and open-label active-controlled, parallel-group, multicenter, 12-week dose-ranging trials, treatment with Fp MDPI was compared to treatment with Fp DPI in patients whose asthma was poorly controlled on non-ICS treatments (Study 201 [N = 640]) or on high-dose ICS (Study 202 [N = 640]). The results suggested no difference between treatments for the change in trough forced expiratory volume in one second (FEV_1) at 12 weeks for similar doses of Fp MDPI and Fp DPI 100 mcg and 250 mcg.
3. Two phase III, randomized controlled trials (RCTs) (Study 301 [N = 647] and Study 30017 [N = 728]) demonstrated that Fp MDPI is superior to placebo with respect to improving trough FEV_1 values at 12 weeks. In one 26-week, open-label, active-comparator RCT designed to evaluate safety (Study 305 [N = 674]), Fp MDPI was noninferior to Fp (Flovent) hydrofluoroalkane (HFA) for short-term spirometry results, although this was neither a primary nor a secondary outcome and there were methodologic limitations such as the use of pooled medium- and high-dose data sets for primary analyses.
4. A manufacturer-provided indirect comparison suggested that [redacted]
5. Fp MDPI does not address any identified need that is not currently met by alternative ICS monotherapies that are reimbursed for the treatment of asthma.

Implementation Considerations

- CDEC noted that Fp MDPI is the second Fp-containing product approved for use for the treatment of patients with asthma, and that several ICS monotherapies are available in Canada for the treatment of asthma. Given the relatively short duration of the trials (12 weeks) and the choice of placebo as a comparator in trials that assessed efficacy, there is some uncertainty regarding the comparative relative long-term effects of Fp MDPI. Furthermore, there was insufficient evidence from direct comparisons with other ICS monotherapies to assess the potential benefits of Fp MDPI with respect to patient adherence to treatment, ease of use, or satisfaction with Fp MDPI. For these reasons, in order to provide value to public drug plans, Fp MDPI should provide cost savings relative to other ICS therapies currently reimbursed for asthma across all ICS dosage levels (low, medium, and high).
- CDEC noted that patient and provider education on the use of Fp MDPI will be necessary to ensure that this product is used effectively and to avoid potential confusion regarding the dosage of Fp MDPI compared with other Fp-containing products, especially if patients are switched between these products.

Discussion Points:

[redacted]

- There is limited evidence available to compare the safety of Fp MDPI with multiple other monotherapy ICS options available in Canada for the treatment of asthma. In the aforementioned safety trial, Study 305, the incidence of adverse events (AEs) in patients treated with Fp MDPI was similar to that for Fp HFA. Serious adverse events (SAEs) were rare and did not suggest any association with specific treatments. However, longer-term comparative studies of relevant harms are currently lacking, and [redacted]

Background:

Fp MDPI has a Health Canada indication for the maintenance treatment of steroid-responsive bronchial asthma as a prophylactic therapy in patients 12 years of age and older. Fp MDPI is an ICS with Health Canada–approved doses of 55 mcg, 113 mcg, or 232 mcg inhaled orally twice daily.

Summary of CDEC Considerations:

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of Fp MDPI, an indirect comparison and network meta-analyses submitted by the manufacturer, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with steroid-responsive bronchial asthma, and patient group–submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information

Two patient groups, Asthma Canada and The Lung Association – Ontario, provided input for this submission. Patient perspectives were obtained from six online surveys, two phone interviews, input from a certified respiratory educator, selected peer-reviewed studies, and a requested medical briefing from Teva Canada. The following is a summary of key input from the perspective of the patient groups:

- Patients with asthma experience numerous symptoms, including shortness of breath, chronic cough, wheezing, and nighttime waking. For those with moderate-to-severe asthma, the impact is more significant, and can include restricted engagement in physical and social activity, lost productivity, avoidance of the outdoors, and depression and anxiety.
- Current therapies do provide some relief from symptoms; however, patients often report feeling that they do not have control over their disease. They also reported AEs associated with current treatments, such as hoarse voice, increased mucus, low energy and fatigue, appetite loss, and impact on mood. Patients also cited the affordability and financial burden of current treatments as challenges.
- Patients reported symptom control as an important expected outcome for new therapies. They further noted a desire for decreasing the frequency of exacerbations, minimizing physician office and hospital visits, having fewer absences from school and work, and stopping the progression of asthma.
- None of the patients surveyed had direct experience with Fp MDPI. Survey respondents indicated interest in a product that is easier to administer, as well as an inhaler that can provide consistent dosing with active metering.

Clinical Trials

The CDR systematic review included three RCTs. Two trials — Study 301 and Study 30017 — were double-blind, placebo-controlled, randomized trials that evaluated Fp MDPI at 55 mcg, 113 mcg, and 232 mcg twice daily compared with placebo for up to

12 weeks. Both efficacy trials were identical in design; however, each assessed different doses of Fp MDPI. In one trial, patients were assigned to low-dose (55 mcg) Fp MDPI, medium-dose (113 mcg) Fp MDPI, or placebo twice daily; in the second trial, patients were assigned to medium-dose (113 mcg) Fp MDPI, high-dose (232 mcg) Fp MDPI, or placebo twice daily. The studies also included groups treated with Fp/salmeterol (FS) MDPI fixed-dose combination. Evidence related to this product is considered separately from Fp MDPI.

The third trial (305: N=674) was an open-label, active-controlled trial that was primarily a safety study, but also evaluated the noninferiority of the pooled arms of Fp MDPI 113 mcg and 232 mcg twice daily compared with the pooled arms of Fp HFA 110 mcg and 220 mcg twice daily with respect to change from baseline in trough FEV_1 at 26 weeks.

All trials included patients at least 12 years of age with prior treatment of ICS or ICS/long-acting beta-2 agonist at a qualifying dosage and a diagnosis of asthma present for at least three months with no exacerbations or changes to medications for at least one month prior to consent being given.

Limitations of the RCTs included the relatively short duration of follow-up; there were higher numbers of premature withdrawals in the placebo arms of the efficacy studies than in the Fp MDPI arms, which were generally due to worsening asthma; and the only phase III head-to-head comparative evidence was provided by the safety study (Study 305) versus Fp HFA. Therefore, there are uncertainties in understanding the comparative dosing, efficacy, and safety versus other ICS products. As well, patients appeared to have received suboptimal ICS treatment prior to randomization into the placebo-controlled efficacy studies, meaning the treatment effect with Fp MDPI may have been relatively overestimated. Generalizability of the results from the three RCTs is also uncertain because the patients enrolled were predominantly white with a mean age ranging from 38 years to 46 years.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- change in pulmonary function (i.e., FEV_1)
- health-related quality of life (i.e., Asthma Quality of Life Questionnaire [AQLQ])
- control of asthma symptoms (i.e., total daily asthma symptoms score)
- use of rescue medications (i.e., weekly average of the total daily use of albuterol or salbutamol)
- health care resource utilization (i.e., hospitalization, emergency room visits, physician visits)
- SAEs, total AEs, and withdrawals due to AEs

The primary efficacy outcome for all three trials was a change from baseline in trough FEV_1 over time.

Efficacy

- Fp MDPI used twice daily demonstrated greater improvement in trough FEV_1 compared with placebo at all strengths within 12 weeks. Mean differences between treatments were:
    - Fp MDPI 55 mcg versus placebo
        - Study 301: 0.119 L (95% confidence interval [CI], 0.025 to 0.212; *P* = 0.0132)
    - Fp MDPI 113 mcg versus placebo
        - Study 301: 0.151 L (95% CI, 0.057 to 0.244; *P* = 0.0017)
        - Study 30017: 0.123 L (95% CI, 0.038 to 0.208; *P* = 0.0047)
    - Fp MDPI 232 mcg versus placebo
        - Study 30017: 0.183 L (95% CI, 0.098 to 0.268; *P* < 0.0001)
    - Little evidence is available on the minimal clinically important difference (MCID) for FEV_1, yet the between-group differences were below the minimum patient perceivable improvement values reported in the literature (0.23 L) and below the MCID suggested by the Health Canada reviewer (0.20 L).
- Fp MDPI 113 mcg and 232 mcg twice daily were noninferior with respect to the change from baseline in trough FEV_1 to Fp HFA 110 mcg and 220 mcg twice daily (mean difference –0.002 L [95% CI, –0.068 to 0.065]), in which the lower limit of the 95% CI did not fall below the pre-specified –0.125 L noninferiority margin over a 26-week period.

- Fp MDPI had an inconsistent effect on improvement of AQLQ compared with placebo. Mean differences between treatments were:
  - Fp MDPI 113 mcg versus placebo
    - Study 301: 0.301 (95% CI, 0.094 to 0.508; *P* = 0.0044)
    - Study 30017: 0.131 (95% CI, –0.068 to 0.330; *P* = 0.1962)
  - Fp MDPI 232 mcg versus placebo
    - Study 30017: 0.216 (95% CI, 0.017 to 0.415; *P* = 0.0334)
  - None of the mean differences met the 0.5 MCID threshold to be considered clinically significant
  - Statistically significant differences in the Fp MDPI 55 mcg arm could not be concluded in accordance with the fixed-sequence testing procedure.
- Fp MDPI demonstrated a greater improvement in total daily asthma symptoms scores over weeks one to 12 compared with placebo. Mean differences between treatments were:
  - Fp MDPI 113 mcg versus placebo
    - Study 301: –0.165 (95% CI, –0.251 to –0.080; *P* = 0.0002)
    - Study 30017: –0.195 (95% CI, –0.288 to –0.102; *P* < 0.0001)
  - Fp MDPI 232 mcg versus placebo
    - Study 30017: –0.156 (95% CI, –0.248 to –0.063; *P* = 0.0010)
  - Statistically significant differences in the Fp MDPI 55 mcg arm could not be concluded in accordance with the fixed-sequence testing procedure.
- Fp MDPI showed a greater improvement in the weekly average of total daily use of rescue medication compared with the placebo group. Mean differences between treatments were:
  - Fp MDPI 55 mcg versus placebo
    - Study 301: –0.464 (95% CI, –0.718 to –0.211; *P* = 0.0003)
  - Fp MDPI 113 mcg versus placebo
    - Study 301: –0.463 (95% CI, –0.716 to –0.209; *P* = 0.0004)
    - Study 30017: –0.607 (95% CI, –0.908 to –0.307; *P* = 0.0001)
  - Fp MDPI 232 mcg versus placebo
    - Study 30017: –0.702 (95% CI, –1.001 to –0.403; *P* < 0.0001)
- Patients taking Fp MDPI had similar outcomes to Fp HFA with respect to health care resource use, and the reported average amount of resource use was high across different areas of health care in Study 305 over 26 weeks:
  - Patients with an unscheduled or outpatient visit
    - 24% in the Fp MDPI 113 mcg group versus 29% in the Fp HFA 110 mcg group
    - 32% in the Fp MDPI 232 mcg group versus 27% in the Fp HFA 220 mcg group
  - Patients with an emergency department or urgent care facility visit
    - 14% in the Fp MDPI 113 mcg group versus 17% in the Fp HFA 110 mcg group
    - 14% in the Fp MDPI 232 mcg group versus 10% in the Fp HFA 220 mcg group
  - Patients with a hospital visit
    - < 1% in the Fp MDPI 113 mcg group versus 5% in the Fp HFA 110 mcg group
    - 3% in the Fp MDPI 232 mcg group versus 5% in the Fp HFA 220 mcg group

Harms (Safety and Tolerability)

- There were similar proportions of patients with SAEs while taking Fp MDPI compared with placebo in study 301 (<1% versus 2%) and study 30017 (<1% versus <1%), as well as compared with Fp HFA in study 305 (6% versus 6%).
- The proportion of patients experiencing AEs overall was similar in those taking Fp MDPI compared with placebo in study 301 (33% versus 36%) and study 30017 (39% versus 36%) as well as compared with Fp HFA in study 305 (67% versus 70%).
- The proportions of patients who withdrew due to AEs were lower between Fp MDPI groups and placebo in study 301 (1% versus 5%) and study 30017 (<1% versus 1%). The most frequently reported AE leading to withdrawal in both placebo groups was asthma (1%). In study 305, withdrawals due to AEs in Fp MDPI compared with Fp HFA were rare (<1% versus 2%).
- The most frequently reported AEs across treatment groups were headache (5%), nasopharyngitis (5%), and upper respiratory tract infection (4%).

Indirect Treatment Comparisons

An indirect treatment comparison was submitted by the manufacturer, which compared the efficacy of Fp MDPI against ICS and ICS/long-acting beta-2 agonist treatments currently available for the treatment of asthma. The analysis was generally supportive of

the conclusion that Fp MDPI was well-tolerated and more efficacious than placebo. [redacted]

Additional Clinical Data

Supportive data from phase I and phase II studies were also discussed by CDEC. Study 10042 was a phase I, multi-center, open-label, randomized, active-controlled, four-period crossover, single-dose study (N = 40) designed to determine the pharmacokinetics and tolerability of high dose Fp MDPI (or FS MDPI) compared to high dose Fp DPI (or FS DPI) in patients with asthma. Two phase II trials, Studies 201 (N = 622) and 202 (N = 640), were randomized, double-blind placebo- and open-label active-controlled, parallel-group, multicenter, 12-week dose-ranging trials in patients with asthma aged 12 years and older. Patients had to have a best FEV_1 of 40% to 85% predicted and demonstrated post-bronchodilator reversibility (≥15% in Study 201 and ≥12% in Study 202). Study 201 was conducted in patients with asthma who were uncontrolled on non-steroidal maintenance therapy, whereas Study 202 was conducted in patients with asthma who remained symptomatic despite high-dose ICS therapy.

In Study 10042, following a single dose administration of Fp MDPI (200 mcg, 1 inhalation) compared to Fp DPI (250 mcg, 2 inhalations), the systemic steroid exposure (measured as peak plasma concentration and the area under the curve at different time points) to Fp was 20% to 30% lower with Fp MDPI than with Fp DPI.

In Study 201, the mean change from baseline in trough FEV_1 values were statistically significantly different for Fp MDPI 25 mcg, 50 mcg, and 100 mcg twice daily, as well as for Fp DPI 100 mcg twice daily compared to placebo; no statistically significant differences were observed between any dose of Fp MDPI and Fp DPI 100 mcg twice daily. In Study 202, the primary analysis, which was the trend test of linear log-dose response in change from baseline in trough FEV_1 over 12 weeks, did not show statistically significant differences between Fp MDPI doses. Therefore, based on the hierarchical analysis plan, planned comparisons between the doses of Fp MDPI and placebo could not be interpreted with respect to statistical significance. There were no statistically significant differences observed with any of the four Fp MDPI doses compared to Fp DPI 250 mcg twice daily; however, this comparison was not adjusted for multiplicity. Comparisons between Fp DPI 250 mcg BID were not statistically significantly different, which raises questions about assay sensitivity of the study. Large percentages of patients in the placebo groups relative to the FP MDPI groups prematurely discontinued treatment in both studies.

Cost and Cost-Effectiveness

The submitted price for a 60-dose pack of Fp MDPI is $16.96 for 55 mcg, $30.96 for 113 mcg, and $48.15 for 232 mcg. At the recommended dose administration of one inhalation twice daily, with strength depending on disease severity, Fp MDPI costs between $206 and $586 per patient, per year.

The manufacturer submitted a cost-minimization analysis comparing the drug acquisition cost of Fp MDPI with a market share–based weighted average drug acquisition cost of Fp Diskus and Fp HFA. The manufacturer undertook a secondary analysis comparing Fp MDPI to all other available ICS therapies. The analyses were conducted from the perspective of a Canadian public health care payer over a one-year time horizon, with drug prices for comparators obtained from the Ontario public drug plan formulary. The choice of a cost-minimization analysis was justified based on a claim of similar efficacy and safety with other ICS inhalers supported by a head-to-head RCT comparing Fp MDPI to Fp HFA, and an indirect comparison comparing Fp MDPI to other ICS inhalers. The manufacturer reported that Fp MDPI ($548) was associated with an annual cost savings of $191 per patient, per year when compared with a market share–based weighted average of Fp HFA and Fp Diskus ($739; a 26% reduction in drug costs). In the secondary analysis comparing Fp MDPI to the market share–weighted cost of all ICS inhalers, Fp MDPI had an annual cost savings per patient of $193 ($497 versus $690; a 28% reduction in drug costs).

CDR identified the following key limitations and issues for consideration with the manufacturer's submission:

- The use of a market share–based weighted approach using utilization data from several provinces for an average annual cost of Fp HFA and Fp DPI was not considered appropriate for the base-case analysis. Analyses against the individual comparators should have been presented in the base case.

- As indicated in the CADTH Clinical Review Report, [redacted]
- CADTH clinical reviewers concluded that there is limited comparative evidence for the use of Fp MDPI versus alternative ICS therapies, including dose equivalency and efficacy equivalency, based on limitations with the phase II studies presented in support of establishing comparative safety and efficacy between Fp MDPI and Fp DPI. Therefore, the results of an assessment of comparative costs between Fp MDPI and other ICS treatments are uncertain.The clinical expert consulted by CDR indicated there is the potential for overuse if double the numbers of actuations of Fp MDPI per day are used to match the usual Fp dose, which would negate cost savings and may lead to increased costs.

CDR reanalyses suggested that Fp MDPI ($206 to $586 per patient, per year) may be less costly than most currently available ICS treatments ($124 to $1,331 per patient, per year) based on publically available prices at assumed relative low, medium and high doses.

July 18, 2018 Meeting

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None

December 12, 2018 Meeting

CDEC Members:

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Ms. Heather Neville, Mr. Allen Lefebvre, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None