CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

FLUTICASONE PROPIONATE/SALMETEROL XINAFOATE (ARBESDA 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/salmeterol xinafoate multidose dry powder inhaler be reimbursed for the maintenance treatment of asthma in patients 12 years of age or older, if the following condition is met:

Condition
Fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler should provide cost savings for drug plans relative to the lowest priced alternative inhaled corticosteroid/long-acting beta-2 agonist combinations reimbursed for the treatment of asthma.

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Fluticasone propionate/ salmeterol xinafoate (Arbesda 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/salmeterol xinafoate multidose dry powder inhaler (FS MDPI) be reimbursed for the maintenance treatment of asthma in patients 12 years of age or older, if the following condition is met:

Condition

- FS MDPI should provide cost savings for drug plans relative to the lowest priced alternative inhaled corticosteroid/long-acting beta-2 agonist combinations (ICS/LABA) 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]), FS MDPI was associated with systemic exposure of fluticasone propionate (Fp) that was similar to that observed with FS dry powder inhaler (DPI; Advair Diskus).
2. In one phase II, randomized, double-blind placebo- and open-label active-controlled, cross-over, multicenter, 12-week dose-ranging, supportive trial (FSS-201 [N = 72]), treatment with FS MDPI was compared to treatment with FS DPI in patients whose asthma was poorly controlled. The results suggested no statistically significant differences between medium-doses of FS MDPI and FS DPI 100 mcg/50 mcg for change in the area under the curve for baseline adjusted forced expiratory volume in one second (FEV_1) measurements from pre dose to 12 hours post dose ($AUC_{0\text{-}12h}$) values at 12 weeks.
3. Two phase III, randomized controlled trials (RCTs) (Study 301 [N = 647] and Study 30017 [N = 728]) demonstrated that FS MDPI is superior to placebo and Fp MDPI monotherapy 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]), FS MDPI was noninferior to FS DPI 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. FS MDPI does not address any identified need that is not currently met by alternative ICS/LABA therapies that are reimbursed for the treatment of asthma.

Implementation Considerations

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

Discussion Points

[redacted]

- There is limited evidence available to compare the safety of FS MDPI with multiple other ICS/LABA 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 FS MDPI was similar to that for FS DPI. 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

FS MDPI has a Health Canada indication for the treatment of asthma in patients 12 years of age and older. FS MDPI is a fixed-dose combination of an ICS, fluticasone propionate, and a LABA, salmeterol xinafoate. The Health Canada–approved dosages are 55 mcg/14 mcg, 113 mcg/14 mcg, or 232 mcg/14 mcg inhaled orally twice daily.

Summary of CDEC Considerations

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a manufacturer-completed template of RCTs of FS 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

Three patient groups — Asthma Canada, the British Columbia Lung Association, and The Lung Association – Ontario — provided input for this submission. Patient perspectives were obtained from seven online surveys, two phone interviews, input from a certified respiratory educator, 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 night-time 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/or work, and stopping the progression of asthma.
- Two survey respondents reported using FS MDPI as part of a clinical trial or through other means. Both patients described ease of use and consistent, active metering. Other survey respondents indicated interest in an inhaler that can provide consistent dosing with active metering, and easy administration.

Clinical Trials

The systematic review included three RCTs. Two trials — Study 301 and Study 30017 — were double-blind, active- and placebo-controlled randomized trials that evaluated FS MDPI at 55 mcg/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg twice daily compared

with placebo for up to 12 weeks. Both efficacy trials were identical in design; however, each assessed different dosages of FS MDPI. In one trial, patients were assigned to low-dose (55 mcg/14 mcg) FS MDPI, medium-dose (113 mcg/14 mcg) FS MDPI, or placebo, twice daily; in the second trial, patients were assigned to medium-dose (113 mcg/14 mcg) FS MDPI, high-dose (232 mcg/14 mcg) FS MDPI, or placebo, twice daily. The studies also included groups treated with Fp MDPI monotherapy. Evidence related to this product is considered separately from FS MDPI.

The third trial, Study 305, was an open-label, active-controlled trial. While it was primarily a safety study, Study 305 also evaluated the noninferiority of the pooled arms of FS MDPI 113 mcg/14 mcg and 232 mcg/14 mcg twice daily compared with the pooled arms of FS DPI 250 mcg/50 mcg and 500 mcg/50 mcg twice daily with respect to change from baseline in trough FEV_1 at 26 weeks.

All trials included patients who were at least 12 years of age and had prior treatment of ICS or ICS/LABA 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 FS 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 FS DPI. Therefore, there are uncertainties in understanding comparative dosing, efficacy, and safety versus other ICS/LABA products. As well, patients appeared to have received suboptimal ICS treatment prior to randomization into the placebo-controlled efficacy studies; therefore, the treatment effect with FS MDPI may have been relatively overestimated. Generalizability of the results from the three RCTs is also uncertain because 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)
- 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

- FS MDPI used twice daily demonstrated greater improvement in trough FEV_1 compared with placebo at all strengths within 12 weeks. The mean differences between treatments were:
    - FS MDPI 55 mcg/14 mcg versus placebo:
        - Study 301: 0.266 L (95% confidence interval [CI], 0.172 to 0.360; P <0.0001)
    - FS MDPI 113 mcg/14 mcg versus placebo:
        - Study 301: 0.262 L (95% CI, 0.168 to 0.356; P < 0.0001)
        - Study 30017: 0.274 L (95% CI, 0.189 to 0.360; P < 0.0001)
    - FS MDPI 232 mcg/14 mcg versus placebo:
        - Study 30017: 0.276 L (95% CI, 0.191 to 0.361; P < 0.0001)
    - Little evidence is available on the minimal clinically important difference (MCID) for FEV_1. However, the between-group differences were greater than the minimum patient perceivable improvement values reported in the literature (0.23 L) and the MCID suggested by the Health Canada review (0.20 L).
- In Study 305, FS MDPI 113 mcg/14 mcg and 232 mcg/14 mcg twice daily were noninferior with respect to the change from baseline in trough FEV_1 to FS DPI 250 mcg/50 mcg and 500 mcg/50 mcg twice daily (mean difference 0.029 L [95% CI, −0.036 to 0.095]), 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.

- FS MDPI had a significant effect on improvement of responses to the Asthma Quality of Life Questionnaire compared with placebo. The mean differences between treatments were:
  - FS MDPI 55 mcg/14 mcg versus placebo:
    - Study 301: 0.332 (95% CI, 0.125 to 0.540; *P* = 0.0017)
  - FS MDPI 113 mcg/14 mcg versus placebo:
    - Study 301: 0.608 (95% CI, 0.402 to 0.814; *P* < 0.0001)
    - Study 30017: 0.681 (95% CI, 0.478 to 0.885; *P* < 0.0001)
  - FS MDPI 232 mcg/14 mcg versus placebo:
    - Study 30017: 0.623 (95% CI, 0.418 to 0.828; *P* < 0.0001)
- FS MDPI demonstrated a greater improvement in total daily asthma symptoms scores over weeks 1 to 12 compared with placebo. The mean differences between treatments were:
  - FS MDPI 55 mcg/14 mcg versus placebo:
    - Study 301: −0.194 (95% CI, −0.279 to −0.109; *P* < 0.0001)
  - FS MDPI 113 mcg/14 mcg versus placebo:
    - Study 301: −0.230 (95% CI, −0.315 to −0.144; *P* < 0.0001)
    - Study 30017: −0.277 (95% CI, −0.370 to −0.184; *P* < 0.0001)
  - FS MDPI 232 mcg/14 mcg versus placebo:
    - Study 30017: −0.304 (95% CI, −0.397 to −0.212; *P* < 0.0001).
- FS MDPI showed a greater improvement in the weekly mean number of inhalations of rescue medication compared with the placebo arm. The mean differences between treatments were:
  - FS MDPI 55 mcg/14 mcg versus placebo:
    - Study 301: −0.704 (95% CI, −0.957 to −0.450; *P* < 0.0001)
  - FS MDPI 113 mcg/14 mcg versus placebo:
    - Study 301: −0.675 (95% CI, −0.928 to −0.421; *P* < 0.0001)
    - Study 30017: −0.989 (95% CI, −1.291 to −0.686; *P* < 0.0001)
  - FS MDPI 232 mcg/14 mcg versus placebo:
    - Study 30017: −1.066 (95% CI, −1.365 to −0.766; *P* < 0.0001).
- Patients taking FS MDPI had similar outcomes to those taking FS DPI with respect to health care resource use. 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:
    - 32% in the FS MDPI 113 mcg/14 mcg arm versus 18% in the FS DPI 250 mcg/50 mcg arm
    - 31% in the FS MDPI 232 mcg/14 mcg arm versus 25% in the FS DPI 500 mcg/50 mcg arm
  - Patients with an emergency department or urgent care facility visit:
    - 18% in the FS MDPI 113 mcg/14 mcg arm versus 5% in the FS DPI 250 mcg/50 mcg arm
    - 15% in the FS MDPI 232 mcg/14 mcg arm versus 11% in the FS DPI 500 mcg/50 mcg arm
  - Patients with a hospital visit:
    - 3% in the FS MDPI 113 mcg/14 mcg arm versus zero in the FS DPI 250 mcg/50 mcg arm
    - 5% in the FS MDPI 232 mcg/14 mcg arm versus 2% in the FS DPI 500 mcg/50 mcg arm.

Harms (Safety and Tolerability)

- In all three trials, the frequency of patients reporting SAEs while taking FS MDPI was similar to those taking placebo in Study 301 (< 1% versus 0) and Study 30017 (1% versus < 1%), as well as compared with FS DPI in Study 305 (≤ 9% versus ≤ 7%).
- The proportion of patients experiencing AEs overall was similar in those taking FS MDPI (41% to 42%) compared with placebo (36%), as well as compared with FS DPI in Study 305 (70% versus 69%).
- The proportion of patients who withdrew due to AEs was lower between FS MDPI arms and placebo in Study 301 (1% versus 5%) and Study 30017 (2% versus 1%). In Study 305, withdrawals due to AEs were lower in FS MDPI arms compared with FS DPI arms (1% versus 4%).
- The proportion of patients experiencing at least one asthma exacerbation was similar between patients treated with FS MDPI 113 mcg/14 mcg (11%) and those treated with FS DPI 250 mcg/50 mcg (12%); however, it was higher in patients treated with FS MDPI 232 mcg/14 mcg compared with FS DPI 500 mcg/50 mcg (15% versus 7%).
- The most frequently reported AEs across treatment arms were nasopharyngitis, headache, and upper respiratory tract infection.

Indirect Treatment Comparisons

An indirect treatment comparison was submitted by the manufacturer, which compared the efficacy of FS MDPI against ICS and other ICS/LABA treatments currently available for the treatment of asthma. The analysis was generally supportive of the conclusion that FS MDPI was more efficacious than placebo and well tolerated. [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 and FS MDPI compared to high dose Fp DPI and FS DPI in patients with asthma. One phase II trial, Studies FSS-201 (N = 72), was a randomized, double-blind placebo- and open-label active-controlled, cross-over, multicenter, 12-week, single-dose dose-ranging trial in patients with asthma aged 12 years and older who were uncontrolled on asthma therapies. Patients had to have a best FEV_1 of 40% to 85% predicted and demonstrated post-bronchodilator reversibility (15% or greater).

In Study 10042, following a single dose administration of FS MDPI (200 mcg/12.5mcg, 1 inhalation) compared to Fp DPI (500 mcg/50 mcg, 1 inhalation), the systemic steroid exposure (measured as peak plasma concentration and the area under the curve at different time points) to Fp was similar between the two. Regarding the concentration of salmeterol xinafoate, the systemic exposure was approximately 20% to 50% lower with FS MDPI compared to FS DPI.

In Study FSS-201, the mean change in baseline-adjusted FEV_1 $AUC_{0\text{-}12h}$ from baseline to week 12 values were statistically significantly higher for all FS MDPI doses (100 mcg/6.25 mg, 100 mcg/12.5 mg, 100 mcg/25 mg, 100 mcg/50 mg) compared with Fp MDPI 100 mcg. The FS MDPI 100 mcg/12.5 mcg and 100 mcg/25 mcg groups were not found to be statistically significantly different from the FS DPI 100 mcg/50 mcg groups for this efficacy outcome. The FS MDPI 100 mcg/12.5 mcg (metered dose: 113 mcg/14 mcg) is the Health Canada recommended strength of FS MDPI.

Cost and Cost-Effectiveness

The submitted price of FS MDPI per inhaler (60 actuations) is $61.04 per 55 mcg/14 mcg inhaler, $73.0740 per 113 mcg/14 mcg inhaler, and $103.7340 per 232 mcg/14 mcg inhaler. At the recommended dosage of two inhalations per day, the daily cost is $2.03 to $3.46. The manufacturer submitted a cost analysis comparing FS MDPI with currently reimbursed fluticasone propionate and salmeterol xinafoate medications as individual products (e.g., non-combination inhalers). At the submitted price for each dose strength at assumed relative low, medium and high doses, FS MDPI would represent cost savings ranging from $0.66 to $1.30 per day when compared with the publicly available total daily drug costs of fluticasone propionate and salmeterol xinafoate. FS MDPI would also represent cost savings when compared with other ICS/LABA combination product inhalers, excluding the budesonide/formoterol combination product inhaler.

CDR identified the following considerations:

[redacted]

- It is difficult to draw any definitive conclusions on the comparative costs given the uncertainty associated with the comparative clinical efficacy data and the paucity of data regarding equivalent dosages of FS MDPI with other ICS/LABA inhalers.
- The use of FS MDPI may lead to savings in dispensing fees compared with the use of the individual component medications (i.e., two inhalers).

- The clinical expert consulted by CDR indicated that there is the potential for overuse if double the number of actuations of FS MDPI per day are used to match the usual FS dose. This would negate cost savings and could lead to increased costs.

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