Fluticasone furoate/Vilanterol (Breo Ellipta)

National PBM Drug Monograph

VA Pharmacy Benefits Management Services,   
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions.  These documents will be updated when new data warrant additional formulary discussion.  Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Executive Summary**

* Fluticasone furoate/vilanterol (FF/VI) is a combination inhaled corticosteroid/long-acting beta-agonist inhaler (ICS/LABA) that is administered once daily. Fluticasone furoate is a salt-form that allows for once daily dosing. Vilanterol is a novel once daily LABA.
* FF/VI is FDA-approved 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. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.
* FF/VI is administered via a breath-actuated multi-dose dry powder inhaler. The dose is 100/25mcg once daily.
* There are 4 primary studies (two 6-month and two 1-year) conducted in patients with COPD comparing 3 strengths of FF/VI (200/25, 100/25, and 50/25), the individual components, and placebo. The primary endpoints for the 6-month trials were mean FEV1 0-4 hours post-dose and change from baseline trough FEV1. For the 1-year trials, the primary outcome was the annual rate of moderate and severe COPD exacerbations. At the time of this writing, only the two 6-month trials have been published.
* In the 6-month trials, the mean treatment difference between FF/VI 100/25 and placebo was 173 and 214mL. The mean treatment difference for trough FEV1 was 115 and 144mL. The magnitude of change versus the individual components was smaller.
* Average rescue inhaler use was reduced by 0.71-0.89 puffs/day with FF/VI 100/25 compared to placebo. The magnitude of change versus the individual components was smaller.
* Greater improvement in symptoms (e.g., cough, sputum, breathlessness, nighttime awakening due to COPD, symptom, rescue-free days, etc.) was observed with FF/VI 100/25 compared to placebo. Significance versus the individual components varied between studies and symptoms
* Dyspnea was assessed in the 6-month trials using the dyspnea domain of the Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS). The minimal clinically important difference is considered to be 0.5 units. None of the comparisons achieved this difference.
* In the 1-year exacerbation trials, the mean annual rate of exacerbation in study 102970 was 0.9 with the approved dose of FF/VI versus 1.14 with vilanterol alone. In study 102871, the rates were 0.70 and 1.05 respectivley.
* There are 3 supportive studies of 3-months duration that compared the marketed strength of FF/VI 100/25 to fluticasone/salmeterol 250/50 and 500/50. Pulmonary function studies (FEV1 0-24 hours) showed the treatment difference was statistically significant in 1 of the 3 trials.
* In the 6-month trials, the incidence of any treatment-related adverse events (AEs), discontinuations due to AEs, or serious AEs were similar between FF/VI 100/25 and the individual components and placebo; for the 1-year trials, the incidence for FF/VI 100/25 was similar to VI 25 alone. There incidence of AEs in the 1-year trials was higher than that of the 6-month trials.
* Adverse events with an incidence of ≥3% that were common to both the 6-month and 1-year trials were nasopharyngitis, headache, upper respiratory tract infection, and oral/oropharyngeal candidiasis.
* The incidence of pneumonia in the 1-year trials was 5.9-6.8% (all FF/VI doses) versus 3.3% with vilanterol alone in the 1-year trials. Pneumonia was fatal in 1 patient receiving FF/VI 100/25 and 7 receiving FF/VI 200/25.
* There was a higher incidence of bone fracture in patients receiving FF/VI (2% each in the 50/25, 100/25, and 200/25 groups vs. 1% vilanterol alone). Typically, corticosteroid-associated fractures tend to occur in the lumbar/thoracic spine or pelvis/hip. The majority of fractures reported in the FF/VI trials were considered to be traumatic and occurred mainly in the upper and lower extremities.
* Cardiac: In the 6-month trials, mean maximum post-baseline changes in QTc(F) and percentage of patients with QTc(F) > 30msec were similar for all active treatments and placebo. No patient had a QTc(F) > 500msec. Similar results were observed in the active treatment groups in the 1-year trials. Approximately half the patients in the 6-month trials underwent 24-hour Holter monitoring. The frequency of abnormalities of potential clinical significance was 13-15% (all FF/VI groups), 11% (VI only), 6-14% (FF only), and 10% (placebo).
* The only comparative safety data available at this time is from the 12-week trial comparing FF/VI 100/25 QD to FP/SAL 500/50 BID. The AE profiles were similar although more local steroid effects were seen with FP/SAL (4% vs. 1%) and more CV effects were seen with FF/VI (3% vs. <1%).
* Fluticasone/vilanterol has the advantage of once daily dosing; however, long-term data and comparative studies are limited.

**Introduction**

Fluticasone furoate/vilanterol (FF/VI) is the first combination ICS/LABA inhaler to be dosed once daily. This is a new salt form for fluticasone allowing for once daily administration (fluticasone propionate is administered twice daily) and vilanterol is a novel LABA. These 2 drugs are available in the US as a combination product and not as their separate entities.

**Pharmacokinetics**

Pharmacokinetic parameters are shown in **Table 1**. The area under the curve (AUC) for fluticasone was 46% lower in patients with COPD compared to healthy volunteers. Conversely, AUC for vilanterol was 24% higher in patients with COPD compared to healthy volunteers. No dosage adjustment is needed based on age (>65 years), ethnicity, gender renal impairment, or mild hepatic impairment. Caution should be used in patients with moderate-severe hepatic impairment.

**Table 1: Pharmacokinetics of Fluticasone Furoate and Vilanterol**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Route of administration** | **Fluticasone furoate** | **Vilanterol** |
| Time to peak plasma concentration | Inhaled | 0.5-1hrs | 10 min |
| Absolute bioavailability | Inhaled | 15.2% | 27.3% |
| Oral bioavailability (swallowed portion) | Inhaled | ~1.3% | <2% |
| Volume of distribution | IV | 66L | 165L |
| Protein binding | IV | 99.6% | 93.9% |
| Metabolism |  | CY3A4 (metabolites decreased activity) | CY3A4 (metabolites decreased activity) |
| Elimination | Oral | Primarily via feces | Urine ~70%; feces~30% |
| Half-life | Repeat dose inhaled | 24 hrs | 21.3hrs |

Information obtained from product package insert

**FDA Approved Indication(s)**

Fluticasone furoate/vilanterol is approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.

This product is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

**Potential Off-Label Uses**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) (available on the VA PBM Intranet site only).

* Treatment of asthma (the asthma clinical development program is in progress; several trials have been published)

**Current VA Formulary Alternatives**

* The VA has a National Contract for budesonide/formoterol (Symbicort)
* Mometasone and formoterol as separate inhalers

**Dosing/Administration**

One oral inhalation of 100/25mcg once daily and should be taken at the same time every day.

**Dosage Form/Strengths and Handling**

FF/VI is available via a multi-dose dry powder inhaler containing 100mcg of fluticasone furoate and 25mcg of vilanterol. Each inhaler is preloaded with 30 doses of the drug. The inhaler has a dose indicator that shows the number of remaining doses.

Store FF/VI in a dry place between 68-77°F; excursions between 59-86°F are permitted. FF/VI is supplied in a moisture protective foil tray. The inhaler should be discarded 6 weeks after opening the foil tray or when the dose counter reads “0”, whichever comes first.

**Efficacy**

This review will only discuss use in COPD and will not address studies conducted in patients with asthma. The clinical trial development program for COPD consists of the studies shown in **Table 2**. At the time of this writing, 4 trials have been published; the small 4-week trial by Lotvall compared an unapproved dose (FF/VI 400/25) to placebo and will not be further discussed. Information for the remaining trials was obtained from the FDA review.

**Table 2: Clinical Trials in COPD**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **n** | **Duration** | **Type of Study** | **Treatment Arms** |
| Primary Studies | Kerwin 2013  Martinez 2013  Study 102970  Study 102871 | 1030  1224  1633  1622 | 6-months  6-months  1-year  1-year | Lung function study  Lung function study  Exacerbation study  Exacerbation study | FF/VI 100/25; FF/VI 50/25; FF 100; VI 25; PBO  FF/VI 200/25; FF/VI 100/25; FF200; FF100; VI25; PBO  FF/VI 200/25; FF/VI 100/25; FF/VI 50/25; VI 25  FF/VI 200/25; FF/VI 100/25; FF/VI 50/25; VI 25 |
| Supporting Studies | Study 110946  Lotvall 2012  Agusti 2013  Study 113109  Study 112352 | 54  60  528  519  511 | 4-weeks  4-weeks  3-months  3-months  3-months | Serial FEV1 study  Safety and efficacy  Comparator vs. FP/SAL  Comparator vs. FP/SAL  Comparator vs. FP/SAL | FF/VI 100/25; FF/VI 50/25; FF/VI 200/25; PBO  FF/VI 400/25; PBO  FF/VI 100/25; FP/SAL 500/50  FF/VI 100/25; FP/SAL 250/50  FF/VI 100/25; FP/SAL 250/50 |

*Pulmonary function*

6-month trials

Patients were required to have a post bronchodilator FEV1/FVC ratio ≤ 0.70, post bronchodilator FEV1 ≤ 70% predicted, Modified Medical Research Council (mMRC) dyspnea score ≥ 2, and 10 pack-year smoking history.

The primary endpoints for the 6-month trials were mean FEV1 0-4 hours post-dose on day 168 and change from baseline trough FEV1 on day 169.

The mean demographic and baseline characteristics of patients include: 62.1 years old, 70% male, 84% Caucasian, BMI 26.3, 54% current smokers, pack-years smoking history 44.1, post-albuterol FEV1% predicted 48.1, 24% had ≥ 1 moderate COPD exacerbation and 9% had ≥ 1 severe exacerbation.

In Kerwin et al., statistical analysis for the effect on pulmonary function was limited to comparing FF/VI 100/25 to placebo, FF100, VI25 and VI25 to placebo. FEV1 (0-4h) was significantly greater with FF/VI 100/25 compared to FF100 and placebo; the difference versus VI25 was not significant. Mean trough FEV1 was significantly greater with FF/VI 100/25 compared to placebo; the comparisons versus FF100 and VI25 were not significant.

In Martinez et al, statistical comparisons were limited to FF/VI 200/25 versus placebo, FF200, VI25 and VI25 vs. placebo. Mean FEV1 (0-4h) was significantly greater with FF/VI 200/25 compared to FF200 and placebo; the difference versus VI25 was not significant. Mean trough FEV1 was significantly greater with FF/VI 200/25 compared to placebo; the comparisons versus FF200 and VI25 were not significant. In both studies, VI25 was significantly better than placebo for both FEV1 endpoints.

Although the study by Martinez did not provide a statistical analysis for the FF/VI 100/25 strength, the improvement in FEV1 endpoints was similar to the improvement observed in the Kerwin trial.

1-year trials

Patients had to have the same entry requirements as in the 6-month studies plus a history of ≥ 1 moderate/severe exacerbation in the previous 12 months. The primary endpoint was the annual rate of moderate and severe COPD exacerbations. Trough FEV1 was a secondary endpoint.

The mean demographic and baseline characteristics of patients include: 63.7 years old, 57% male, 84% Caucasian, BMI 26.9, 44% current smokers, pack-years smoking history 46.2, post-albuterol FEV1% predicted 45.4, ≥ 1 moderate COPD exacerbation 92%, and ≥ 1 severe exacerbation 20%.

The point estimate for trough FEV1 was estimated from a Forest Plot shown in the FDA review. FF/VI was compared to VI alone. The contribution an ICS has when added to a bronchodilator on pulmonary function is small as shown in **Table 3**.

3-month comparator trials (supportive studies)

These trials compared the approved dose of FF/VI 100/25 to fluticasone/salmeterol 250/50 and 500/50. The primary endpoint was FEV1 (0-24 hours). The treatment difference was statistically significant in only 1 of the 3 trials.

**Table 3: Improvement in Pulmonary Function**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Duration** | **Comparisons** | **Treatment Difference [95% CI]** | |
| **FEV1 (0-4h)** | **Trough FEV1** |
| Kerwin | 6-months | FF/VI 100/25 vs. FF100  FF/VI 100/25 vs.VI 25  FF/VI 100/25 vs. PBO  FF/VI 50/25 vs.VI 25  FF/VI 50/25 vs. PBO  VI 25 vs. PBO  FF100 vs. PBO | 120 [70, 170]\*  71 [21, 121]  173 [123, 224]\*  90 [39, 140]  192 [141, 243]  103 [52, 153]\*  53 [3, 104] | 82 [28, 136]  48 [-6, 102]  115 [60, 169]\*  62 [8, 117]  129 [74, 184]  67 [12, 121]\*  33 [-22, 88] |
| Martinez | 6-months | FF/VI 100/25 vs. FF100  FF/VI 100/25 vs.VI 25  FF/VI 100/25 vs. PBO  FF/VI 200/25 vs.FF200  FF/VI 200/25 vs. VI 25  FF/VI 200/25 vs. PBO  VI 25 vs. PBO  FF100 vs. PBO  FF200 vs. PBO | 168 [116, 220]  29 [-23, 81]  214 [161, 266]  168 [117, 219]\*  24 [-27, 75]  209 [157, 261]\*  185 [133, 237]\*  46 [-6, 98]  41 [-11, 93] | 100 [47, 152]  45 [8, 97]  144 [91, 197]  123 [72, 174]  32 [-19, 83]  131 [80, 183]\*  100 [48, 151]\*  44 [-8, 97]  8 [-44, 60] |
| 102970ⱡ | 1-year | FF/VI 100/25 vs.VI 25  FF/VI 200/25 vs. VI 25  FF/VI 50/25 vs.VI 25 | Not evaluated | 25 [CI crossed 0]  25 [CI crossed 0]  30 |
| 102871ⱡ | 1-year | FF/VI 100/25 vs.VI 25  FF/VI 200/25 vs. VI 25  FF/VI 50/25 vs.VI 25 | Not evaluated | 55  65  45 |
| **Study** | **Duration** | **Comparisons** | **FEV1 (0-24h) Treatment Diff [95%CI]** | |
| Agusti | 3-month | FF/VI 100/25 vs. FP/SAL 500/50 | 22 [-18, 63] | |
| Study 113109 | 3-month | FF/VI 100/25 vs. FP/SAL 250/50 | 29 [-22, 80] | |
| Study 112352 | 3-month | FF/VI 100/25 vs. FP/SAL 250/50 | 80 [37, 124]\* | |

Abbreviations: CI=confidence interval; FEV1=forced expiratory volume in 1 second; FF=fluticasone furoate; FF/VI=fluticasone furoate/vilanterol; FP/SAL=fluticasone propionate/salmeterol; PBO=placebo; VI=vilanterol

ⱡ Results for the 1-year studies were estimated from Forest plot

\*Significant difference (in Kerwin statistical comparisons were conducted for FF/VI 100/25 and in Martinez for FF/VI 200/25 versus their individual components and placebo)

*Dyspnea*

The Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnea domain was a secondary endpoint in the 6-month trials. The minimal clinically important difference is considered to be 0.5 units. None of the comparisons achieved this difference.

*Symptomatic endpoints assessed by diary card*

Changes in symptomatic endpoints for the marketed dose FF/VI 100/25 versus the individual components are shown in **Table 4**. For the differences, 95% confidence intervals were calculated (asterisked results indicate comparisons where the 95% confidence excluded zero). Compared to placebo, greater improvements (CI excludes zero) were observed for FF/VI 100/25. Improvement varied when FF/VI was compared to the individual components.

**Table 4: Symptomatic Endpoints in 6-Month Trials**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Comparisons** | **Cough** | **Sputum** | **Breathless-ness** | **Rescue use** | **Nighttime awakenings req. rescue use** | **Rescue-free 24h periods** | **AM PEF**  **(L/min)** |
| Kerwin | FF/VI 100/25 vs. PBO  FF/VI 100/25 vs. VI  FF/VI 100/25 vs. FF 100 | -0.20\*  -0.07  -0.11\* | -0.11\*  -0.06  -0.04 | -0.31\*  -0.12  -0.19\* | -0.89\*  -0.34\*  -0.53\* | -0.14\*  -0.08  -0.08 | 18.95\*  7.95\*  12.99\* | 25.2\*  5.7  17.7\* |
| Martinez | FF/VI 100/25 vs. PBO  FF/VI 100/25 vs. VI  FF/VI 100/25 vs. FF 100 | -0.13\*  -0.06  -0.10\* | -0.14\*  -0.12\*  -0.11\* | -0.31\*  -0.12\*  -0.21\* | -0.71\*  -0.27\*  -0.53\* | -0.20\*  -0.08  -0.08 | 13.54\*  8.64\*  13.62\* | 21.7\*  5.8  12.7\* |

\*Comparisons where the 95%CI excludes zero

For the 1-year trials, the mean rescue inhaler use and nighttime awakenings due to COPD symptoms was lower with the combination groups compared to VI alone (data shown graphically in FDA review).

*COPD Exacerbations*

The two 1-year trials were designed to evaluate the impact FF/VI has on the rate of moderate and severe COPD exacerbations. The primary outcome was the annual rate of moderate-severe exacerbations. Time to first moderate or severe exacerbation and annual rate of corticosteroid-treated exacerbations also were assessed

COPD exacerbations were defined as worsening of ≥ 2 major symptoms (dyspnea, cough, sputum volume, sputum purulence) or any 1 major symptom plus any 1 of the following minor symptoms (sore throat, colds, fever without other cause, and increased cough to wheeze for at least 2 consecutive days). Exacerbations were classified as moderate if treatment with systemic steroids and/or antibiotics was required and severe if hospitalization was required.

The integrated study results showed that FF/VI 50/25, 100/25, and 200/25 reduced the annual rate of moderate/severe exacerbations by 16%, 27%, and 23% respectively versus vilanterol alone. Individual study results are shown in **Table 5**. The risk of time to first moderate-severe exacerbation was reduced by 24% with FF/VI 100/25 versus vilanterol alone.

**Table 5: Moderate-Severe COPD Exacerbations in 1-year Trials**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **N** | **Treatment Arms** | **Mean Annual Rate (exacerbations/year)** | **Ratio vs. VI**  **[95%CI]** |
| Study 102970 | 1633 | FF/VI 100/25 (n=403)  FF/VI 200/25 (n=409)  FF/VI 50/25 (n=412)  VI 25 (n=409) | 0.90  0.79  0.92  1.14 | 0.79 [0.64, 0.97]  0.69 [0.56, 0.85]  0.81 [0.66, 0.99]  - |
| Study 102871 | 1622 | FF/VI 100/25 (n=403)  FF/VI 200/25 (n=402)  FF/VI 50/25 (n=408)  VI 25 (n=409) | 0.70  0.90  0.92  1.05 | 0.66 [0.54, 0.81]  0.85 [0.70, 1.04]  0.87 [0.72, 1.06]  - |

Information obtained from product package insert

COPD exacerbations were also evaluated in the 6-month trials as part of routine adverse event monitoring (**Table 6**). The majority of exacerbations were considered moderate, most resolved, and none were fatal. In Kerwin et al, both doses of the combination resulted in fewer patients with ≥ 1 exacerbation compared to placebo and the individual component groups. In Martinez et al., there were more patients with ≥ 1 exacerbation in both combination groups than in the steroid alone groups; however, both combination groups had fewer exacerbations compared to vilanterol alone and placebo.

**Table 6: COPD Exacerbations in 6-month Trials**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Kerwin** | | | | | **Martinez** | | | | | |
| **FF/VI 100/25** | **FF/VI**  **50/25** | **FF100** | **VI25** | **PBO** | **FF/VI 200/25** | **FF/VI 100/25** | **FF100** | **FF200** | **VI25** | **PBO** |
| Pts. with ≥ 1 exacerbation  n (%) | 18 (9) | 12 (6) | 26 (13) | 22 (11) | 21 (10) | 14 (7) | 13 (6) | 4 (2) | 10 (5) | 18 (9) | 21 (10) |
| **Exacerbation (n):**  Moderate  Severe | 15  4 | 12  0 | 23  3 | 15  7 | 18  3 | 8  6 | 8  5 | 4  0 | 7  3 | 11  7 | 15  6 |
| **Outcome (n)**  Resolved  Fatal  Not resolved at d/c from study | 19  0  0 | 10  0  2 | 25  0  1 | 21  0  1 | 21  0  0 | 13  0  1 | 12  0  1 | 4  0  0 | 10  0  0 | 18  0  0 | 20  0  1 |

*Long-term Trials*

The SUMMIT trial is a long-term randomized, placebo-controlled trial that will evaluate the impact of FF/VI (100/25mcg) and the individual components on survival in patients with moderate COPD (n=16,000) who have either a history of CVD or are at increased risk for CVD. The primary outcome is mortality; secondary outcomes include FEV1 and effect on a composite CV end-point. The estimated study completion date is July 2015.

**Adverse Events (Safety Data)**

For the approved dose in the 6-month trials, 9% of patients discontinued the trial due to an AE and 6% had a serious AE. The incidence in the 1-year trials was 8% and 15% respectively. Two patients in the 6-month trials and 10 patients in the 1-year trials had an on or post-treatment fatal SAE. Incidences reported for all treatment arms are shown in **Table 7.**  The exposure-adjusted rate of death (integrated 6-month and 1-year trials) was lowest with the fluticasone only arms. Among the 3 doses of FF/VI, the lowest rate was with the approved dose (14.3) versus 12.0 with placebo.

**Table 7: Adverse Events: Integrated Results for 6-Month and 1-Year Trials**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **6-month Trials** | | | | | | | | | | | **1-year Trials** | | | | | |
| **FF/VI**  **100/25** | **FF/VI**  **50/25** | | **FF/VI**  **200/25** | **VI 25** | | **FF100** | | **FF200** | **PBO** | | **FF/VI**  **100/25** | | **FF/VI**  **50/25** | **FF/VI**  **200/25** | | **VI 25** |
| N | 410 | 206 | | 205 | 408 | | 410 | | 203 | 412 | | 806 | | 820 | 811 | | 818 |
| Any on-tx AE | 203 (50) | 144 (55) | | 93 (45) | 196 (48) | | 201 (49) | | 96 (47) | 196 (48) | | 621 (77) | | 620 (76) | 622 (77) | | 575 (70) |
| D/C due to AE | 36 (9) | 19 (9) | | 23 (11) | 40 (10) | | 37 (9) | | 15 (7) | 39 (9) | | 62 (8) | | 53 (8) | 61 (8) | | 45 (6) |
| Any on-tx SAE | 23 (6) | 6 (3) | | 15 (7) | 31 (8) | | 22 (5) | | 10 (5) | 21 (5) | | 123 (15) | | 136 (17) | 124 (15) | | 126 (15) |
| Any on or post-tx fatal SAE | 2 (<1) | 2 (<1) | | 1 (<1) | 3 (<1) | | 1 (<1) | | 0 | 2 (<1) | | 10 (1) | | 16 (2) | 14 (2) | | 13 (2) |
|  | **Integrated 6-month AND 1-year Trials** | | | | | | | | | | | | | | | | |
| **FF/VI**  **100/25** | | **FF/VI**  **50/25** | | | **FF/VI**  **200/25** | | **VI 25** | | | **FF100** | | **FF200** | | | **PBO** | |
| Any fatal event exposure-adjusted rate | 14.3 | | 23.4 | | | 19.5 | | 19.3 | | | 6.4 | | 0 | | | 12.0 | |

Data obtained from FDA review

Adverse events reported in the 6-month and 1-month studies with an incidence of ≥ 3% were nasopharyngitis, headache, upper respiratory tract infection, and oral/oropharyngeal candidiasis (**Table 8**). The incidence of these AEs, except for headache, was higher in the 1-year studies.

**Table 8: Adverse Events with Incidence ≥3%: Integrated Results for 6-month and 1-year Trials**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **6-month Trials** | | | | | | | **1-year Trials** | | | |
| **FF/VI**  **100/25** | **FF/VI**  **50/25** | **FF/VI**  **200/25** | **VI 25** | **FF100** | **FF200** | **PBO** | **FF/VI**  **100/25** | **FF/VI**  **50/25** | **FF/VI**  **200/25** | **VI 25** |
| N | 410 | 206 | 205 | 408 | 410 | 203 | 412 | 806 | 820 | 811 | 818 |
| Nasopharyngitis | 35 (9) | 14 (7) | 13 (6) | 41 (10) | 32 (8) | 20 (10) | 31 (8) | 128 (16) | 112 (14) | 158 (19) | 112 (14) |
| Headache | 29 (7) | 12 (6) | 15 (7) | 36 (9) | 30 (7) | 11 (5) | 20 (5) | 57 (7) | 61 (7) | 67 (8) | 60 (7) |
| URI | 29 (7) | 16 (8) | 7 (3) | 20 (5) | 16 (4) | 5 (2) | 13 (3) | 90 (11) | 84 (10) | 75 (9) | 78 (10) |
| Oral/oropharyngeal  candidiasis | 22 (5) | 20 (10) | 9 (4) | 9 (2) | 13 (3) | 13 (6) | 9 (2) | 87 (11) | 110 (13) | 88 (11) | 55 (7) |

Data obtained from FDA review

The only comparative safety data available at this time is from the 12-week trial comparing FF/VI 100/25 QD to FP/SAL 500/50 BID. The AE profiles were similar although more local steroid effects were seen with FP/SAL (4% vs. 1%) and more CV effects were seen with FF/VI (3% vs. <1%). Adverse CV events reported in the FF/VI group, hypertension (n=2), atrial fibrillation (n=2), tachycardia (n=2), angina pectoris (n=1), bradycardia (n=1), coronary artery disease (n=1), and peripheral edema (n=1). In the FP/SAL group, the only CV AE reported was 1 case of hypertension. Results of other comparative trials are needed to determine if there are differences in CV safety.

*Adverse Events of Special Interest*

Adverse events that are specific to corticosteroids and beta-agonists are discussed.

* Pneumonia: The overall incidence was low; 1.5-2% (all active treatments) versus 0.7% with placebo in the 6-month trials and 5.9-6.8% (all FF/VI doses) versus 3.3% with vilanterol alone in the 1-year trials. One patient receiving FF/VI 100/25 and 7 receiving FF/VI 200/25 died in the 1-year trials **Table 9**.

The incidence of pneumonia reported in the 1-year trials is comparable to that reported in the 1-year trials for Advair and Symbicort.

**Table 9: Incidence of Pneumonia:** **Integrated Results for 6-Month and 1-Year Trials**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **6-month Trials** | | | | | | | **1-year Trials** | | | | |
| **FF/VI**  **100/25** | **FF/VI**  **50/25** | **FF/VI**  **200/25** | **VI 25** | **FF100** | **FF200** | **PBO** | | **FF/VI**  **100/25** | **FF/VI**  **50/25** | **FF/VI**  **200/25** | **VI 25** |
| N | 410 | 206 | 205 | 408 | 410 | 203 | 412 | | 806 | 820 | 811 | 818 |
| Any AE of pneumonia | 6 (1.5) | 3 (1.5) | 4 (2) | 7 (1.7) | 6 (1.5) | 3 (1.5) | 3 (0.7) | | 51 (6.3) | 48 (5.9) | 55 (6.8) | 27 (3.3) |
| Serious pneumonia | 1 (0.2) | 1 (0.5) | 3 (1.5) | 5 (1.2) | 3 (0.7) | 2 (1.0) | 1 (0.2) | |  |  |  |  |
| Fatal pneumonia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 1 (0.1) | 0 | 7 (0.9) | 0 |

Data obtained from FDA review and product package insert

* Ocular Effects: Use of FF/VI did not increase the incidence of glaucoma, increased IOP, and cataracts based on the two 1-year trials. Ocular effects were reported 0.9%, 1%, 0.9%, and 1% of patients in the FF/VI 50/25, 100/25, 200/25, and vilanterol groups respectively. PI
* Bone Fracture: There was a higher incidence of bone fracture in patients receiving FF/VI (2% each in the 50/25, 100/25, and 200/25 groups vs. 1% vilanterol alone). Typically, corticosteroid-associated fractures tend to occur in the lumbar/thoracic spine or pelvis/hip. The majority of fractures reported in the FF/VI trials were considered to be traumatic and occurred mainly in the upper and lower extremities.
* Cardiac: In the 6-month trials, mean maximum post-baseline changes in QTc(F) and percentage of patients with QTc(F) > 30msec were similar for all active treatments and placebo. No patient had a QTc(F) > 500msec. Similar results were observed in the active treatment groups in the 1-year trials.

Approximately half the patients in the 6-month trials underwent 24-hour Holter monitoring. The frequency of abnormalities of potential clinical significance was 13-15% (all FF/VI groups), 11% (VI only), 6-14% (FF only), and 10% (placebo). The most frequently reported abnormalities are shown in **Table 10**.

**Table 10: 24-Hour Holter Monitor Findings in 6-Month Trials**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **FF/VI**  **100/25** | **FF/VI**  **50/25** | **FF/VI**  **200/25** | **VI 25** | **FF100** | **FF200** | **PBO** |
| N | 188 | 98 | 98 | 191 | 184 | 89 | 168 |
| Ventricular arrhythmias, all n(%)   * Sustained VT * Non-sustained VT | 12 (6)  0  12 (6) | 7 (7)  0  6 (6) | 8 (8)  0  7 (7) | 15 (8)  0  15 (8) | 13 (7)  0  13 (7) | 3 (3)  1 (1)  1 (1) | 10 (6)  0  9 (5) |
| Supraventricular arrhythmias, all n(%)   * Sustained SVT * Atrial fibrillation * Atrial flutter | 6 (3)  3 (2)  3 (2)  0 | 1 (1)  0  0  1 (1) | 2 (2)  1 (1)  1 (1)  0 | 5 (3)  1 (<1)  4 (2)  0 | 5 (3)  3 (2)  4 (2)  1 (<1) | 1 (1)  1 (1)  0  0 | 1 (<1)  0  1 (<1)  0 |

Data obtained from FDA review

Routine cardiovascular AE monitoring in the 6-month trials found similar rates for the marketed dose of FF/VI (100/25) and placebo. In the 1-year trials, patients received FF/VI or VI. Rates for CV AEs were similar. Changes in blood pressure and pulse rate from baseline were small and changes were similar in all treatment groups in the 6-month and 1-year trials.

* HPA-axis: In both 6-month studies, 24 h urinary cortisol (UC) excretion was measured at baseline and at the end of the study in a subset of patients (n=700). The UC excretion ratio for each of the groups was close to 1.0 and there were no significant differences between any of the active arms versus placebo.

In the supporting study 110946, 24-hour serum cortisol (considered to be a more reliable measure than 24-h UC excretion) was evaluated in 54 patients with COPD. This study showed no effect on serum cortisol after 28 days of treatment with FF/VI 50/25, 100/25, and 200/25.

A formal HPA-axis study conducted in patients asthma (n=185) was used to support the safety of FF/VI in patients with COPD because the systemic exposure to FF is higher in patients with asthma than with COPD. Twenty-four hour serial serum cortisol was measured at baseline and at day 42. This was a non-inferiority study comparing FF/VI 100/25, FF/VI 200/25, and prednisolone 10mg to placebo. In order to demonstrate non-inferiority, the lower bound of the confidence interval had to be greater than 0.8. Treatment ratio relative to placebo for FF/VI 100/25 was 0.99 [95%CI 0.87, 1.12] and FF/VI 200/25 was 0.97 [95%CI 0.86, 1.10] demonstrating non-inferiority of both FF/VI doses to placebo. The treatment ratio of prednisolone to placebo was 0.34 [95% CI 0.28, 0.41] indicating reduced serum cortisol.

**Contraindications**

* Severe hypersensitivity to mild proteins
* Hypersensitivity to fluticasone furoate, vilanterol or any of the excipients

**Warnings and Precautions**

*Consult product package insert for further information and instructions*

Asthma-related death

Deterioration of disease and acute episodes

Excessive use of FF/VI and use with other long-acting beta-agonists

Local effects of corticosteroids

Pneumonia

Immunosuppression

Transferring patients from systemic corticosteroid therapy

Hypercorticism and adrenal suppression

Drug Interactions with strong CYP P450 3A4 inhibitors

Paradoxical Bronchospasm

Hypersensitivity reactions

Cardiovascular Effects

Reduction in bone mineral density

Glaucoma and cataracts

Coexisting conditions

Hypokalemia and hyperglycemia

**Special Populations**

*Pregnancy Category C:* There are no adequate trial data in pregnant women. In laboratory animals, systemic administration of corticosteroids and beta-agonists has been shown to be teratogenic. There were no teratogenic effects noted in rats and rabbits receiving inhaled FF/VI, FF, or VI at doses that exceed human doses, with the exception of fetal skeletal variation (i.e., decreased or absent ossification in cervical vertebral centrum and metacarpals) in rabbits with VI at 1000x the maximum recommended human daily dose . FF/VI should be used during pregnancy only if the potential benefits justify potential risk to the fetus.

*Nursing Women:* It is unknown if FF/VI is excreted in human breast milk. Because other corticosteroids and beta-agonists have been detected in human milk, caution should be used when administering FF/VI to nursing women.

*Geriatric Use:* Among the patients participating in the COPD clinical trials, 2,508 and 565 were ≥ 65 and ≥ 75 years old respectively. No overall differences in effectiveness or safety were noted between these patients and younger patients.

**Look-alike / Sound-alike (LASA) Error Risk Potential**

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

**Table 11: Results of LASA Search**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
| Fluticasone furoate/vilanterol  Breo Ellipta | None  None | None  None | None  None | Fluticasone/salmeterol  None |

**Drug Interactions**

* Both fluticasone and vilanterol are substrates of CYP3A4. Concomitant administration of ketoconazole (potent CYP3A4 inhibitor) increases systemic exposure to fluticasone and vilanterol. Exercise caution when considering coadministration of FF/VI with ketoconazole or other strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole)
* Beta2-agonists, including vilanterol, should be administered with extreme caution to patients receiving MAOIs, tricyclic antidepressants, or drugs known to prolong QTc interval or within 2 weeks of discontinuation of such drugs. The effect of beta-agonists on the cardiovascular system may be potentiated by these agents. Drugs that prolong the QTc interval have an increased risk of ventricular arrhythmias.
* Beta blockers can block the pulmonary effects of beta agonists and may produce severe bronchospasm in patients with reversible obstructive airway disease. Therefore, patients with COPD should not normally be treated with beta- blockers. If there are no acceptable alternatives to the use of beta-blockers for these patients, cardioselective beta-blockers could be considered and used with caution.
* The use of beta-agonists can acutely worsen hypokalemia that may occur with non-potassium-sparing diuretics. Although the clinical significance of these effects is not known, caution should be used in codministration of these agents.

**Comparative Cost**

Please refer to VA pricing sources for updated information.

**Conclusions**

Fluticasone furoate/vilanterol is the first once daily ICS/LABA. It is currently approved for use in COPD. It has been shown to improve pulmonary function and modestly reduce the risk of moderate-severe exacerbations for patients with a post-bronchodilator FEV1 ≤ 70% (mean 45%) and who have had ≥ 1 moderate/severe exacerbation in the prior year. At this time there is only one 12-week trial comparing FF/VI to fluticasone/salmeterol. Longer term comparative trials are needed to determine if there are differences in efficacy and safety among agents in the ICS/LABA class.

**References**

Kerwin EM, Scott-Wilson, Sanford L, et al. A randomized trials of fluticasone furoate/vilanterol (50/25mcg; 100/25

mcg on lung function in COPD. Resp Med 2013; 107: 560-569.

Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25mcg) improves lung function in COPD; a randomized trial. Resp Med 2013; 107: 550-559.

Vestbo J, Anderson J, Brook RD, et al. The study to understand mortality and morbidity in COPD (SUMMIT) study protocol. Eur Respir J 2013; 41 (5):1017-22.

FDA Advisory Committee Meeting Materials <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM347931.pdf>

Allen A, Schenkenberger I, Trivedi R, et al. Inhaled fluticasone furoate/vilanterol does not affect

hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomised, double-blind, placebo-controlled study. Clin Respir J. 2013Oct;7(4):397-406.

Agustí A, de Teresa L, De Backer W, et al.  A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2013 Oct 10. [Epub ahead of print]