

Testimony to the FDA Pulmonary-Allergy Drugs  
Advisory Committee

Fluticasone/Vilanterol (Breo Ellipta)  
NDA 204-275

April 17, 2013

Sammy Almashat, MD, MPH

Michael Carome, MD

Sidney Wolfe, MD

Public Citizen Health Research Group

(We have no financial conflicts of interest)

# Reasons to oppose approval

- Fluticasone/vilanterol (FF/VI) at the dose proposed offers no meaningful additional benefit over vilanterol (VI) alone (which is not being considered for approval) on either a surrogate endpoint (lung function, or FEV1) or a clinical endpoint (COPD exacerbations)
- The addition of such a low-dose of fluticasone confers only additional risks, including pneumonia and bone fractures
- Potential is high for dangerous off-label use of FF/VI in asthmatics (convenient once daily dosing). Unlike current ICS/LABA combinations, FF/VI has never before been approved in asthma and there is limited long-term safety data in this population.

FF/VI offers no clinically  
meaningful benefit over VI alone

# Efficacy:

## Lung function

- Two 24-week placebo-controlled trials in moderate to severe COPD patients served as primary source of data
- Results of two 52-week trials in patients with more severe COPD, and recent history of exacerbations, also pooled to assess for lung function

# Efficacy:

## Lung function

- Does addition of ICS to VI lead to additional benefits on lung function?
- Change in trough FEV1 from baseline is typically used as an indicator of the efficacy of the ICS component in ICS/LABA therapy
- FF/VI failed to provide a statistically significant benefit over VI alone in trough FEV1 in any of the four pivotal trials, at both 24 and 52 weeks

# Efficacy:

## COPD exacerbation frequency

- Two 52-week trials in patients with moderate to severe COPD and at least one exacerbation in the prior 12 months
- Three doses of FF/VI (50/25, 100/25, 200/25) compared with single dose of VI (25)
- Primary outcome: annual rate of moderate to severe COPD exacerbations

# Efficacy:

## COPD exacerbation frequency

- Only one (2970) of the two 52-week trials demonstrated a significant reduction in a dose-response fashion in moderate or severe exacerbations with FF/VI compared with VI alone (FF/VI 100/25: 21% reduction; 95%CI: 3-36)
- The FDA clinical reviewer concluded the following:
  - “While a numeric treatment benefit of FF/VI to VI is seen for all doses in both trials, **the trials fail to provide replicate, statistically significant, improvement for the combination products compared to VI alone.**” (p. 106)

# No clinically meaningful effect on exacerbation frequency in single trial demonstrating statistical benefit

- Statistical reviewer's conclusion:
  - “In [this] study 2970, the mean rate of moderate and severe exacerbation in the VI 25 group is about one exacerbation per year. **For the proposed dose of FF/VI 100/25, the rate of moderate and severe exacerbation is reduced by about a quarter of an event in one year.**” (p. 150)



# Low-dose corticosteroid loses benefits, maintains harms

- The dose of fluticasone chosen for FF/VI (100 mcg total daily dose [TDD]) was much lower than that used in current fluticasone/salmeterol (Advair) formulations (500 mcg TDD)
- This is likely responsible for the lack of additional benefit of FF/VI over VI monotherapy
- This low dose was enough, however, to cause significantly more side effects that were serious

# Low-dose corticosteroid loses benefits, maintains harms

- ICS therapy, while capable of reducing exacerbation incidence at high doses (fluticasone 500 mcg TDD; TORCH trial), loses any meaningful benefit at low doses, while residual ICS harms persist
- This was evident in the current trial, with a similar increase in serious adverse effects, such as pneumonia, at all doses of fluticasone, with very slight, or absent dose-response curves for fluticasone-associated adverse events

Safety concerns

# Safety concerns with FF/VI all related to fluticasone component

- Overall infections
- Pneumonia
- Fractures
- Other concerns (candidiasis and nasopharyngitis)

# Fluticasone dose-*independent* increase in serious, non-fatal infection (SAE) incidence

- Rate of serious infections increased in all three FF/VI arms relative to VI monotherapy in 52-week exacerbation trials
  - 35/820 (4.3%) in FF/VI 50/25
  - 43/806 (5.3%) in FF/VI 100/25 **~ 2x the rate in VI monotherapy**  
(20/818; 2.4%)
  - 37/811 (4.6%) in FF/VI 200/25
- Highest rate of serious infections in FF/VI dose (100/25) proposed for approval due to 6 cases of cellulitis, twice as many as in the rest of the study arms combined

# Fluticasone dose-*independent* increase in serious, non-fatal pneumonia (SAE) incidence

- Consistent with prior data on ICS, pneumonia was, by far, the most common serious infection in 52-week exacerbation trials (X-ray confirmed in 81-93% of cases)
- Virtually identical rates of pneumonia SAEs were present across all three FF/VI arms
  - 22/820 (2.7%) in FF/VI 50/25
  - 21/806 (2.6%) in FF/VI 100/25
  - 21/811 (2.6%) in FF/VI 200/25

**~ 2.6x the rate in VI monotherapy**  
(8/818; 1.0%)

# Very slight dose-dependence in overall pneumonia events

- Number of subjects with pneumonia across three FF/VI arms in 52-week exacerbation trials:
    - 48/820 (5.9%) in FF/VI 50/25
    - 51/806 (6.3%) in FF/VI 100/25
    - 55/811 (6.8%) in FF/VI 200/25
- ~ 2x the rate in VI monotherapy (27/818; 3.3%)

# Pneumonia risk persists largely unchanged even at lowest doses of fluticasone

- Rates of pneumonia in FF/VI arms of 52-week exacerbation trials are similar to those seen in previous trials of much higher (10-20x) total daily dose of fluticasone:
  - TORCH trial: 18-19% of pts on 1000 mcg TDD fluticasone after 3 years
  - Current trials: 6% of pts on 50 and 100 mcg TDD fluticasone after 1 year



# Safety concerns with fluticasone: fractures and other bone disorders

- Incidence of fractures increased across all FF/VI arms in 52-week exacerbation trials
  - 14/820 (1.7%) in FF/VI 50/25
  - **19/806 (2.4%) in FF/VI 100/25**
  - 14/811 (1.7%) in FF/VI 200/25
  - **8/818 (1.0%) in VI 25**
- Dose of FF/VI proposed for approval (100/25) only arm in which fracture incidence was significantly increased compared to VI (25) monotherapy:
  - 2.4% vs. 1.0% – **NNH: 72**

# Other safety concerns in fluticasone arms

- Higher rates of candidiasis in all fluticasone arms in both 24-week lung function and 52-week exacerbation trials
- Higher rates of nasopharyngitis in higher-dose fluticasone arms (100/50 and 200/50 FF/VI) in the 52-week exacerbation trials

# Concerns of off-label use in asthmatics

- FF/VI, if approved, will almost certainly be used off-label in asthmatic patients (convenient once daily dosing)
- Unlike currently available ICS/LABA combination therapies, which were first approved for asthma, the safety profile of FF/VI, which contains a new LABA and a very low dose of fluticasone, in asthmatics will remain uncertain
- The seemingly higher potency of VI compared with salmeterol, evident in the four active comparator trials with Advair, is concerning and, particularly when paired with such a small dose of fluticasone, may plausibly increase mortality in asthmatics (7 of the 13 deaths in asthmatics on salmeterol in the SMART trial were on concomitant ICS therapy, presumably at higher doses than this NDA's proposed fluticasone dose)

# Safety of FF/VI in asthmatics

- GSK dataset: 68 Phase I-III trials of FF/VI in asthma patients
- Highest rate of total and asthma-related hospitalizations seen with proposed dose (100/25) of FF/VI

Data to support NDA approval  
based on unethical clinical trials

# NDA depends upon data gleaned from unethical trials

- As was the case with indacaterol, for which six unethical trials were conducted in support of approval, the trials upon which this NDA is based were unethical, withholding critical therapy from patients in placebo and inhaled corticosteroid (ICS) arms

# Unethical undertreatment: placebo-controlled trials

- Current standard of care (GOLD guidelines) calls for treatment of moderate to very severe COPD, defined as GOLD Stage II-IV (post-bronchodilator FEV1 <80% predicted) with long-acting bronchodilator
- Therapy withheld from 414 patients in placebo arm with moderate to **very severe** COPD (GOLD Stage II-IV) in both 24-week lung function trials:
  - **272 (66%) on no concomitant COPD therapy** for duration
  - 103 (25%) maintained on inadequate therapy with short-acting anticholinergics

# Unethical undertreatment: withholding of long-acting bronchodilators

- Two additional arms in 24-week trials given only ICS therapy (FF 50 and FF 100)
- 818 patients with moderate to **very severe** COPD (GOLD Stage II-IV) randomized to ICS-only arms
  - **590 (72%) on no concomitant continuous bronchodilator therapy**
  - 167 (20%) maintained on inadequate therapy with short-acting anticholinergics



# Over-treatment with unnecessary, risky ICS therapy

- FDA clinical reviewers noted that “...the GOLD guidelines reserve the addition of the ICS to a LABA for patients with Stage 3 disease who have a history of exacerbations.” (p. 82)
- None of the 821 patients randomized to FF/VI arms in the 24-week trials were required to have a recent history of exacerbation (hospitalization for exacerbation within 6 weeks of screening was an exclusion criterion)
  - 377 (46%) had Stage I-II disease

# Conclusions

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Given that FF/VI is not a breakthrough drug and offers no clinically significant advantages over available FDA-approved long-acting bronchodilators or combination therapies, significant weight must be given to any signal suggesting safety concerns

# Conclusions

- “Demonstration of an added benefit [of corticosteroid therapy] is a key requirement for the FF/VI application, particularly given the safety concerns associated with corticosteroids...as a drug class. These concerns include increased risks of pneumonia and bone disorders.”
  - Susan Limb, MD (Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products)

# Conclusions

- Therefore, the central question for approval considerations is whether combination FF/VI, at the dose proposed (100/25), confers any clinically meaningful benefits for COPD patients over and above VI (25) monotherapy to justify the added risks
- The answer is clearly no

# Conclusions

- In addition, further long-term, placebo-controlled, studies of FF/VI, or other COPD therapies, in which subjects with moderate to very severe COPD are randomized to groups that receive substandard (placebo) care for prolonged periods of time, must not be conducted
- Any such trials already underway should be halted