Testimony to the Joint Meeting of FDA's Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committees

Fluticasone furoate/Vilanterol (Breo Ellipta)

sNDA 204-275

March 19, 2015

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(We have no financial conflicts of interest)

Reasons to oppose approval

- Addition of vilanterol (VI) to fluticasone furoate (FF), like previous LABA-containing therapies, increases severe exacerbations in adolescents and should certainly not be approved in this population
- In adults, Breo Ellipta offers no unique advantage on clinical outcomes over currently marketed therapies, while far less is known about risks, especially with regard to asthma-related hospitalizations, intubations, and deaths.
- Much larger safety trials of currently marketed inhaled LABA/ICS therapies render approval of another, novel LABA-containing therapy premature until a similarly expansive study is conducted with FF/VI

Ongoing post-market LABA safety trials in adult and adolescent asthmatics

- Post-marketing requirement, for all LABA manufacturers, to compare the safety of inhaled LABA/ICS to inhaled ICS therapy alone
- Four trials, each with 11,700 adult and adolescent subjects (total n=46,800) treated for 6 months
- Primary endpoint: composite of serious asthma outcomes (asthma-related death, intubation, or hospitalization)
- Trials initiated in 2011 and "FDA expects to receive results in 2017"

Source: FDA Drug Safety Communication, 4-15-2011

Adolescents (ages 12-17)

No consistent contribution of VI towards FEV1 improvement in adolescent subjects

- No benefit of VI on either weighted mean FEV1 (usually associated with VI component) or trough FEV1 (FF component) in subgroup analyses of adolescent subjects in studies 6827, 6829, 6863, and 3091. (forest plots, p. 111-114)
- "[T]here was a numerical trend towards a smaller observed treatment effect in the FF/VI treatment group compared to FF alone in younger patients in all three trials for weighted mean serial FEV1 and in two of the three trials for trough FEV1." The "inability to consistently demonstrate the contribution of a LABA to the combination product in younger patients, even numerically" is concerning, especially "[w]hen considering the typical efficacy of bronchodilators (such as vilanterol)".

  - FDA Medical Review, p. 87

Addition of VI increased asthma exacerbations in adolescent subjects

- Study 6837 – largest number of adolescent subjects for subgroup analysis
- FF/VI vs. FF alone in adolescent subjects:
  - At least one exacerbation: 10% vs. 7%; HR 1.4 (95% CI: 0.6, 3.2)
  - Overall rate of exacerbations: HR 1.6 (95% CI: 0.7, 3.6)
  - Asthma-related hospitalizations: 4/146 vs. 0/129 (FDA Briefing Document, p. 169)

Presentation of differential exacerbation frequency between adolescents and adults in GSK-funded published version of Study 6837

- The sole mention of age as a factor in exacerbation frequency within the main article: “Interactions between treatment and the remaining factors (age, sex and region) were not statistically significant.” [referred readers to the online-only supplement for actual rates]
- No mention of numerical imbalance, within the context of: a) the current study’s lack of power to detect a statistically significant difference in such small subgroups; and b) previously known potential differences (2008 FDA meta-analysis) in LABA-associated exacerbation/mortality between pediatric and adult asthmatic patients
- “It is important to note that the trials were not powered to detect [statistically significant] differences based on subgroup analysis.”

  - FDA Medical Review, p. 39

Bateman ED et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014 Apr;69(4):312-9.

Severe VI-associated exacerbations in adolescents mirror previous studies

- The numerical trend of increased exacerbations with FF/VI is consistent with prior studies of LABA-containing medications in children and adolescent subjects with asthma.
- FDA meta-analysis of 110 trials (n=60,954) of LABAs in asthma (2008)
- Composite endpoint of severe exacerbation (asthma-related death, intubation, and hospitalization)
- Significantly higher risk of severe exacerbations in all subjects, but highest rates in children and adolescents

FDA Meta-Analysis Results: Number of Patients Experiencing Severe Exacerbation (taken from 2/18/2010 FDA Drug Safety Communication)

Patient Population	LABA Patients	Non-LABA Patients	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients (n=60,954)	381	304	2.80	1.11 – 4.49
Patients ages 12 to 17 years (n=6,392)	48	30	**5.57**	0.21 – 10.92
Patients ages 4 to 11 years (n=3,415)	61	39	**14.83**	3.24 – 26.43

Adults (age ≥ 18)

FF/VI in adult asthmatics

- In Study 6837, a slightly lower rate of exacerbations was seen in adult subjects on FF/VI compared with FF alone
- However, FF/VI was not superior (and was numerically inferior) to Advair 250/50 bid in improving both weighted mean and trough FEV1 in both adolescent and adult subjects in Study 3091 (forest plot, p. 114)
- Advair 250/50 bid is currently being studied (along with all other currently marketed LABA-containing therapies) in a long-term safety trial comprising 11,700 adult and adolescent subjects to evaluate its effects on severe asthma exacerbations (by comparison, Study 6837 enrolled just 2,019 subjects)

LABAs in adult asthmatics

- SMART (Chest. 2006 Jan;129(1):15-26)
  - 26,355 subjects with asthma randomized to salmeterol or placebo; 47% on background ICS therapy
  - 13 asthma-related deaths on salmeterol vs. 3 on placebo
    - RR 4.37 (95% CI: 1.25, 15.34)
    - 8 excess deaths per 10,000 patients treated
  - 12 of 13 asthma-related deaths in salmeterol arm were in adults; 7 of 13 were on concomitant ICS therapy

- SNS (BMJ. 1993 Apr 17;306(6884):1034-7)
  - 25,180 subjects with asthma randomized to salmeterol or albuterol; 69% on background ICS therapy
  - 12 asthma-related deaths on salmeterol vs. 2 on placebo
  - RR 3.0 (95% CI: 0.7, 20)

LABAs in adult asthmatics

- Cochrane review of LABAs in adult asthmatics (2014)
- All clinical trials of LABA monotherapy or in combination with ICS through September 2013
- LABA monotherapy vs. placebo
  - Total mortality: OR 1.37 (95% CI: 0.88, 2.13)
  - Asthma death: OR 3.54 (95% CI: 1.36, 9.19)
- LABA/ICS vs. same-dose ICS alone
  - Total mortality: OR 1.42 (95% CI: 0.60, 3.38)
  - Asthma death: OR 7.34 (95% CI: 0.15, 370)

Cochrane Review: Conclusion

"Available evidence from the reviews of randomised trials [comprising more than 60,000 subjects] cannot definitively rule out an increased risk of fatal serious adverse events when regular formoterol or salmeterol was added to an inhaled corticosteroid (as background or randomly assigned treatment) in adults or adolescents with asthma."

African-Americans under-represented in Phase III trials

- SMART: African-Americans had higher rate of salmeterol-associated mortality
  - RR 7.26 (95% CI: 0.89, 58.94) compared with Caucasian RR 5.82 (95% CI: 0.70, 48.37)
  - 27 excess asthma-related deaths per 10,000 pts (6 per 10,000 in Caucasians)
- Disproportionately few African-Americans in FF/VI Phase III trials; comprised just 4% of subjects in largest study and only one to evaluate exacerbations (Study 6837)

Insufficient data to evaluate key safety concerns of LABA therapy for asthma

- Because FDA did not require GSK to conduct a safety trial as large as those (n=11,700 each) required of other, currently marketed LABA-containing therapies, the agency had to rely on a post-hoc meta-analysis of Phase II/III trials of FF/VI to evaluate whether the drug increased the risk of asthma-related death, intubation, and hospitalization
- However, "the trials included in the meta-analysis were not primarily designed or powered for investigating the safety outcomes considered in this meta-analysis."
- Too few asthma-related events of interest occurred in the Phase II/III clinical program, "result[ing] in imprecise estimates of the risk in the FDA meta-analysis."
  - FDA Statistical Review, p. 170

Concerns of off-label use in asthmatic children

- Even if approved only for adults, FF/VI, containing a novel LABA (for asthmatics), may be used off-label in both children and adolescents
- Convenient once daily dosing may be appealing to parents and pediatricians alike
- Especially concerning given findings of increased exacerbations with FF/VI in adolescents and of both increased exacerbations and deaths with other LABA-containing therapies in children and adolescents

Conclusions

Questions 5 and 6 before the committee today are narrowly focused on the efficacy and safety of FF/VI in isolation, as gleaned from the inadequately powered Phase II and III trials on FF/VI. However, the safety of FF/VI in relation to asthma-related hospitalizations, intubations, and death, as assessed in the ongoing, adequately powered post-market LABA trials, has not been and could not be addressed in the much smaller, efficacy-focused pre-approval trials on FF/VI.

Conclusions

Given that several much larger and more adequately powered trials are already well underway for all other LABA and LABA/ICS therapies for asthma, the FDA should wait for the outcome of these trials before approving a drug whose safety is largely uncertain and which offers no efficacy advantage over current therapies (and appears inferior to ADVAIR in improving FEV1 in adolescents).

Conclusions

In addition, a similarly large safety study should be conducted on Breo Ellipta before approval. Requiring the safety trial for Breo Ellipta post-approval would again expose patients to a drug with an inadequate safety base.

The results of a post-approval trial evaluating the critical safety questions surrounding Breo Ellipta would not be available for at least several years after 2017, the expected date for results of trials for similarly effective asthma therapies already on the market.

Conclusions

The most relevant questions for the consideration of approval of Breo Ellipta for asthma are therefore the following:

1. Does Breo Ellipta offer any unique benefits over currently available asthma therapies on the central outcome of exacerbation frequency or severity? No.

2. Does Breo Ellipta confer any unique risks over currently available asthma therapies, especially on the central outcome of severe exacerbation frequency? We will not know until well after the results of the trials for other, currently marketed therapies are finalized.