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Re: NDA 204-275 for fluticasone furoate/vilanterol (proposed trade name: Breo Ellipta)

Dear Drs. Chowdhury and Woodcock:

The comments below from the Public Citizen's Health Research Group are being submitted in follow-up to our testimony<sup>1</sup> presented at the April 17, 2013, meeting of the Food and Drug Administration (FDA) Pulmonary-Allergy Drugs Advisory Committee (PADAC) regarding the new drug application (NDA) combination drug fluticasone furoate/vilanterol (FF/VI; proposed trade name Breo Ellipta). This combination offers no clinically meaningful benefit but clearly causes increased risks compared with the bronchodilator vilanterol alone. We submit that:

- (1) The FDA should reject the April 17 PADAC recommendation to approve FF/VI at the dose proposed (100 mcg fluticasone/25 mcg vilanterol; hereafter referred to as 100/25) for the long-term maintenance treatment of airflow obstruction and the reduction of chronic obstructive pulmonary disease (COPD) exacerbations.
- (2) Further long-term, placebo-controlled, phase 3 studies of FF/VI, in which subjects with moderate-to-very severe COPD are randomized to groups that receive placebo or substandard care for prolonged periods of time, should not be conducted for ethical reasons.

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<sup>1</sup> Almashat S, Carome M, Wolfe S. (Public Citizen's Health Research Group). Testimony on Fluticasone/Vilanterol Combination Therapy to the FDA's Pulmonary-Allergy Drugs Advisory Committee. April 17, 2013. Accessed on April 22, 2013. <http://www.citizen.org/hrg2114>.

## I. Background and overview

The FDA should not approve FF/VI for the treatment of COPD for the following reasons:

- (1) At the dose proposed, FF/VI offers no meaningful additional benefit over vilanterol alone (which is not being considered for approval) on either a surrogate endpoint (lung function, or FEV1) or a clinical endpoint (COPD exacerbations).
- (2) The addition of such a low dose of fluticasone confers only additional serious risks, including pneumonia, bone fractures, oral candidiasis, and nasopharyngitis.
- (3) The addition of a small corticosteroid dose combined with its convenient, once-daily dosing makes off-label use of FF/VI in asthmatics virtually certain. Unlike current inhaled corticosteroid/long-acting beta agonist (ICS/LABA) combinations, FF/VI has never before been approved for asthma and there is limited long-term safety data in this population. In addition, given the known dangers of LABA monotherapy in asthmatics, the seemingly higher potency of vilanterol compared with salmeterol is especially concerning.

Dr. Susan Limb, medical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP), emphasized in the opening memo of the FDA's briefing document to the advisory committee that a necessary prerequisite for approval of the combination drug was a clear demonstration of added benefit over vilanterol monotherapy. In her words, “[d]emonstration 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.”<sup>2</sup>

We argue that the addition of what amounts to a token dose of fluticasone did not confer any such meaningful additional benefit over vilanterol monotherapy, certainly not enough of a benefit to justify the added risks or the increased potential for dangerous off-label use of the combination drug in asthmatics. Therefore, we urge the FDA to reject the NDA for FF/VI in its current form. Below, we expand on our reasons opposing approval, in addition to commenting on the unethical design of two of the four pivotal trials conducted to support approval.

## II. FF/VI offers no clinically meaningful benefit over vilanterol alone

Four clinical trials were designed to test the combination of FF/VI therapy against vilanterol alone for up to one year. The trials were designed to test FF/VI against vilanterol monotherapy on two COPD-related outcomes: (1) lung function, a surrogate marker measured by changes in forced expiratory volume in one second (FEV1), and (2) frequency of COPD exacerbations over the course of a year, the only clinical endpoint.

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<sup>2</sup> FDA Briefing Document for April 17, 2013. Pulmonary Allergy Drugs Advisory Committee meeting to discuss NDA 204-275: fluticasone furoate and vilanterol inhalation powder for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). March 7, 2013. Page 5. Accessed on April 22, 2013. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM347929.pdf>.

Two 24-week trials assessed the effects of FF/VI on lung function, as measured by changes in FEV1 from baseline (hereafter referred to as the “lung function trials”), while two 52-week trials assessed the efficacy of combination therapy against vilanterol alone on the frequency of COPD exacerbations (hereafter referred to as the “exacerbation trials”).

### *Lung function*

Lung function was measured in two 24-week placebo-controlled trials in moderate-to-very-severe COPD (GOLD Stage II-IV) patients without a recent history of exacerbations resulting in hospitalization. (The results of the two 52-week exacerbation trials were also pooled to assess lung function.) The key question for approval purposes was whether the addition of ICS therapy (fluticasone) to vilanterol monotherapy led to additional benefits on lung function. As the FDA noted in its briefing documents, the 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 vilanterol alone in improving trough FEV1 in any of the four pivotal trials, at both 24 and 52 weeks. According to the FDA’s clinical reviewer:<sup>3</sup>

The difference in treatment effect between FF/VI and [vilanterol] for trough FEV1 is consistently demonstrated in [lung function trials] 2206 and 2207 (48 ml and 45 ml); however **neither result is statistically significant**. Similarly, the trough FEV1 results from the exacerbation trial 2871 and 2970 also demonstrate a numeric benefit for the combination product compared to [vilanterol] monotherapy; however, **neither of these results is statistically significant**.

The failure of FF/VI to demonstrate a statistically significant lung function difference over vilanterol in any trial underscores the uncertainty of the claimed numerical benefit over vilanterol. As a surrogate endpoint, lung function as measured in a laboratory must not be the sole basis for approval for the treatment of COPD. Nevertheless, the failure to demonstrate a significant effect of combination FF/VI therapy over vilanterol alone highlights the limited efficacy of fluticasone in augmenting the benefits of vilanterol on this physiologic endpoint.

### *COPD exacerbations*

The efficacy and safety of FF/VI in COPD was further measured in two 52-week trials in patients with moderate-to-severe COPD who had had at least one exacerbation in the prior 12 months. Three doses of FF/VI (fluticasone 50 mcg, 100 mcg, and 200 mcg, each combined with 25 mcg vilanterol) were compared with a single 25 mcg dose of vilanterol. The primary outcome was the annual rate of moderate-to-severe COPD exacerbations experienced by subjects.

Only one (study 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 vilanterol alone (FF/VI 100/25: 21% reduction; 95% CI: 3-36). Thus, the FDA’s clinical reviewer concluded the following:<sup>4</sup>

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<sup>3</sup> FDA Briefing Document, p. 86.

<sup>4</sup> FDA Briefing Document, p. 106.

While a numeric treatment benefit of FF/VI to [vilanterol] is seen for all doses in both trials, **the trials fail to provide replicate, statistically significant, improvement for the combination products compared to [vilanterol] alone.**

In the trial that did demonstrate a significant dose-response reduction in exacerbations with FF/VI over vilanterol, the difference in exacerbation efficacy between the therapies was not clinically meaningful. The FDA's statistical reviewer concluded the following:<sup>5</sup>

In [this] study 2970, the mean rate of moderate and severe exacerbation in the [vilanterol] 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.**

Therefore, on the critical clinical endpoint of the frequency of COPD exacerbations, the addition of fluticasone failed to consistently demonstrate a statistically significant benefit over vilanterol monotherapy, and the slight benefit seen in one of the two trials was not clinically meaningful.

### III. FF/VI only confers added risks over vilanterol monotherapy

The additional safety concerns with FF/VI in comparison with vilanterol monotherapy include an increased risk of pneumonia, bone fractures, oral candidiasis, and nasopharyngitis, all attributed to the fluticasone component. In the cases of serious pneumonia and fracture, fluticasone conferred a similar risk in a dose-*independent* fashion, indicating that the harms of fluticasone therapy can be demonstrated even at the lowest doses administered.

#### *Pneumonia*

Consistent with the known risks of ICS therapy, pneumonia was by far the most common serious infection in the 52-week exacerbation trials. The addition of fluticasone, at all doses, led to a 2.6-fold increase in serious, nonfatal cases of pneumonia compared with vilanterol monotherapy (Table 1). There were virtually identical rates of such pneumonia cases across all three FF/VI arms (50/25, 100/25, 200/25).

**Table 1: Rates of serious pneumonia<sup>6</sup>**

Arm	Rates of serious pneumonia
FF/VI 50/25	2.7% (22/820)
FF/VI 100/25	2.6% (21/806)
FF/VI 200/25	2.6% (21/811)
Vilanterol 25	1.0% (8/818)

There was a very slight dose-dependent increase in overall pneumonia events (both serious and non-serious) with FF/VI compared with vilanterol monotherapy in the 52-week trials (Table 2).

<sup>5</sup> FDA Briefing Document, p. 150.

<sup>6</sup> FDA Briefing Document, p. 122-124.

**Table 2: Overall rates of pneumonia (both serious and nonserious cases)<sup>7</sup>**

Arm	Rates of pneumonia
FF/VI 50/25	5.9% (48/820)
FF/VI 100/25	6.3% (51/806)
FF/VI 200/25	6.8% (55/811)
Vilanterol 25	3.3% (27/818)

From these results, the FDA's biometrics reviewer concluded that **for every 33 patients** given FF/VI at the proposed dose of 100/25 mcg, **one additional pneumonia case** would occur beyond that which would occur in patients given vilanterol monotherapy.<sup>8</sup>

The lack of a robust dose-response curve for rates of pneumonia indicates that the pneumonia risk may persist largely unchanged even at the lowest doses of fluticasone. The overall rates of pneumonia in the FF/VI arms of the 52-week exacerbation trials are similar to those seen in previous trials of much higher (10-20x) total daily doses (TDDs) of fluticasone. In the TORCH trials, 18-19 percent of subjects on 1,000 mcg TDD fluticasone acquired pneumonia after three years. In the current trials, approximately 6-7 percent of subjects on 50-200 mcg TDD fluticasone acquired pneumonia after one year.

#### *Bone fractures*

The incidence of bone fractures also increased across all FF/VI arms compared with the vilanterol monotherapy arm in the 52-week exacerbation trials, again in a dose-*independent* fashion (Table 3). The dose of FF/VI proposed for approval (100/25) caused a statistically significant increase in fracture risk compared with vilanterol monotherapy (2.4 percent vs. 1.0 percent, respectively). FDA reviewers concluded that **for every 72 patients** treated with this dose of FF/VI, **one additional fracture** would occur beyond that which would occur in patients given vilanterol monotherapy.

**Table 3: Overall rates of bone fracture (both serious and nonserious cases)<sup>9</sup>**

Arm	Rates of fractures
FF/VI 50/25	1.7% (14/820)
FF/VI 100/25	2.4% (19/806)
FF/VI 200/25	1.7% (14/811)
Vilanterol 25	1.0% (8/818)

#### *Oral candidiasis and nasopharyngitis<sup>10</sup>*

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

<sup>7</sup> FDA Briefing Document, p. 125-126.

<sup>8</sup> FDA Briefing Document, p. 124.

<sup>9</sup> FDA Briefing Document, p. 127.

<sup>10</sup> FDA Briefing Document, p. 133.

#### **IV. Low-dose fluticasone adds only risks, including that of increasing the potential for dangerous off-label use in asthmatics**

The dose of fluticasone chosen for FF/VI (100 mcg 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 vilanterol monotherapy.<sup>11</sup> This low dose was enough, however, to cause a significantly higher rate of serious side effects. This was evident in the current trials, 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. Thus, COPD patients will incur the risks from the addition of fluticasone without clinically meaningful countervailing benefits.

In addition, the low dose of fluticasone tacked on to vilanterol ensures that FF/VI, if approved, will almost certainly be used off-label in asthmatic patients, particularly given its convenient once-daily dosing. The preliminary results of the SMART trial indicated that LABA monotherapy leads to an increased risk of death in asthmatics. The trial was terminated early due to this signal.<sup>12</sup> For this reason, LABA monotherapy is contraindicated in asthma patients.<sup>13</sup> LABA medications are only recommended as second-line therapy when given in combination with ICS treatments.<sup>14</sup>

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. (It should be noted that due to mixed efficacy results for FF/VI in the phase 3 trials for a potential NDA for asthma, GlaxoSmithKline opted not to pursue concurrent approval of FF/VI for asthma.)<sup>15</sup>

The relative doses and potencies of vilanterol and fluticasone in the proposed FF/VI 100/25 formulation also are concerning. The FDA noted in its briefing document that the harms of LABA therapy in asthmatics seem to be dose-related.<sup>16</sup> The apparently greater potency of vilanterol compared with salmeterol, evident in the four active comparator trials with Advair,<sup>17</sup> may correlate with greater beta agonist-related risks, such as asthma-related mortality. Furthermore, it stands to reason that a sufficient

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<sup>11</sup> ICS therapy, while not standard of care for mild (GOLD Stage I) or moderate (Gold Stage II) COPD, is capable of reducing exacerbation incidence at high doses when used in combination with a LABA versus a LABA alone. In the TORCH trial, a fluticasone TDD of 1,000 mcg used in combination with salmeterol resulted in a significant reduction in the rate of moderate or severe exacerbations over three years compared with salmeterol alone. (Table 2 of Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007 Feb 22;356(8):775-89.)

<sup>12</sup> Nelson HS, Weiss ST, Bleecker ER, et al. SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006 Jan;129(1):15-26.

<sup>13</sup> U.S. Department of Health and Human Services. National Institutes of Health (National Heart, Lung, and Blood Institute). Guidelines for the Diagnosis and Management of Asthma. October 2007. Summary Report, p. 40. Accessed on April 29, 2013. <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.htm>.

<sup>14</sup> *Ibid*, p. 42.

<sup>15</sup> See FDA Briefing Document, p. 8-9: “The Division requested that an application for asthma be submitted concurrently with the COPD application, given the novelty of both the [fluticasone] and [vilanterol] components. GSK stated that the recommendation would be taken under advisement. GSK reported mixed efficacy results from the asthma program.”

<sup>16</sup> FDA Briefing Document, p. 7.

<sup>17</sup> FDA Briefing Document, p. 99-102.

dose of ICS therapy is necessary to counteract these harms. The TDD of fluticasone proposed in the current NDA is 100 mcg, lower than all currently approved starting doses of inhaled fluticasone for adult and adolescent (12 years and older) asthma patients, which range from 176 mcg TDD to 1,000 mcg TDD.<sup>18</sup>

Thus, the combination of a novel, high-potency LABA and an unusually small dose of fluticasone may plausibly increase mortality in asthmatics. (Seven 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.)<sup>19</sup>

## V. Ethical concerns with trials conducted in support of the NDA

As was the case with indacaterol,<sup>20</sup> for which six unethical trials were conducted in support of approval, two of the four pivotal trials upon which this FF/VI NDA is based were unethical, withholding critical therapy from patients in placebo and ICS arms. The two 24-week pivotal trials were unethical because investigators withheld effective, standard treatments (including other ICS/LABA therapies) for almost six months from hundreds of subjects with moderate to very severe COPD, instead giving some placebo pills and others substandard care with inhaled steroids alone.

### *Unethical undertreatment in placebo and ICS arms of 24-week trials*

The GOLD guidelines represent the current standard of care for COPD patients.<sup>21</sup> These guidelines call for the treatment of moderate-to-very-severe COPD, defined as GOLD Stage II-IV (post-bronchodilator FEV1 <80% predicted) with a long-acting bronchodilator.<sup>22</sup>

This therapy was withheld from 414 subjects in the placebo arms with moderate-to-**very-severe** COPD in both 24-week lung function trials. Two-thirds (272) of these subjects were given no concomitant COPD

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<sup>18</sup> Low-end of range (176 mcg TDD) gleaned from recommended starting dose for Flovent HFA 44. High-end of range (1,000 mcg TDD) gleaned from recommended starting dose of Advair Diskus 500/50 and Flovent Diskus. Current labels accessed on April 29, 2013, for all fluticasone treatments for asthma: 1) Advair Diskus 100/50, 250/50, 500/50 ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/021077s042lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021077s042lbl.pdf)), 2) Flovent Diskus 50, 100, 250 ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020833s021lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020833s021lbl.pdf)), 3) Advair HFA 45/21, 115/21, 230/21 ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021254s009lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021254s009lbl.pdf)), 4) Flovent HFA 44, 110, 220 ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/021433s019lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021433s019lbl.pdf)).

<sup>19</sup> Table 5 from SMART trial (concomitant asthma meds column): Nelson HS, Weiss ST, Bleecker ER, et al; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006 Jan;129(1):15-26.

<sup>20</sup> Carome M, Wolfe S. (Public Citizen's Health Research Group). Letter to FDA on Indacaterol Maleate (Arcapta Neohaler). March 16, 2011. Accessed on April 22, 2013. <http://www.citizen.org/hrg1938>.

<sup>21</sup> Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (updated 2013). See p.14 for definition of GOLD stages, p.16 for explanation of GOLD groups A-D, and p.36 for treatment recommendations for each Group. Accessed on April 22, 2013. [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2013\\_Feb20.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf).

<sup>22</sup> For Stage II patients, the GOLD guidelines recommend a long-acting bronchodilator only for those with a modified Medical Research Council (mMRC) dyspnea score of  $\geq 2$  (*Ibid*, p. 16, 36). All subjects in the 24-week trials had to have an mMRC  $\geq 2$  as a condition of participation (FDA Briefing Document, p. 67).

therapy for the duration of the trials, while another one-quarter (103) of subjects were maintained on inadequate therapy with short-acting anticholinergics.<sup>23</sup>

Two additional arms in the 24-week trials were given only ICS therapy with fluticasone. Long-acting bronchodilators were withheld for the duration of the trials from 818 subjects with moderate-to-**very-severe** COPD randomized to these ICS-only arms. Seventy-two percent (590) of subjects were on no concomitant continuous bronchodilator therapy during the trials, while another 20 percent (167) of subjects were maintained on inadequate therapy with short-acting anticholinergics.<sup>24</sup>

*Overtreatment with unnecessary, risky ICS therapy*

In addition to withholding of effective treatment from COPD subjects, investigators also subjected other participants with mild to moderate, stable COPD to unnecessary and risky ICS therapy. The FDA's 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."<sup>25</sup>

However, none of the 821 patients randomized to FF/VI therapy 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). Almost half (377) of these subjects had GOLD Stage I-II (mild-to-moderate) disease, for which ICS therapy is not recommended, even in combination with long-acting bronchodilators.<sup>26</sup>

## **VI. Conclusion**

In conclusion, we strongly urge the FDA to reject the NDA for FF/VI. This new combination therapy, arguably never a breakthrough drug to begin with, was conclusively shown to be riskier and not substantially more effective than vilanterol alone in the pivotal trials. It is unacceptable that two of the trials that denied effective treatments to hundreds of severely ill patients for almost half a year were allowed to go forward without objection from either the FDA or local institutional review boards. Any similarly unethical trials currently ongoing should be halted immediately.

Thank you for taking our comments into consideration.

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<sup>23</sup> FDA Briefing Document, p. 83-84.

<sup>24</sup> FDA Briefing Document, p. 83-84.

<sup>25</sup> FDA Briefing Document, p. 82.

<sup>26</sup> Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (updated 2013). See p.14 for definition of GOLD stages, p.16 for explanation of GOLD groups A-D, and p.36 for treatment recommendations for each Group. Accessed on April 22, 2013. [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2013\\_Feb20.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf).