Minutes
Pulmonary & Allergy Drugs Advisory Committee
January 17, 2002
Holiday Inn, Gaithersburg

Flovent Diskus (NDA# 20-833/S-004) and Advair Diskus (NDA# 21-077/S-003) as long-term maintenance therapy in patients with Chronic Obstructive Pulmonary Disease (COPD).

COMMITTEE
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EXECUTIVE SECRETARY
Kimberly Littleton Topper

GUEST SPEAKER (non-voting)
Robert A. Wise, M.D.
Saul Malozowski, M.D., Ph.D.

FDA PARTICIPANTS
Robert Meyer, M.D.
Mary Purucker, M.D.
Ludia Gilbert-McClain, M.D.
Charles Lee, M.D.

I certify that I attended the January 17, 2002 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/	**22 Apr 02**	**/s/**	**22 Apr 02**
Kimberly L. Topper, MS	Date	Mark S. Dykewicz, M.D.	Date
Acting Executive Secretary		Chairman	

A verbatim transcript of this meeting is available for more detailed information.

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Dr. Mark S. Dykewicz called the meeting to order and asked the head table to introduce themselves. Following introductions the Conflict of Interest Statement was read.

Dr. Robert Meyer provided a welcome and introduced the day's topic. He explained the charge to the committee and reminded them that if they recommend approval they are indicating that they believe the sponsor has provided substantial evidence of the safety and efficacy of the two products for the maintenance treatment of COPD, including chronic bronchitis and emphysema, and that they should be labeled and promoted as such. He reminded them that this is not a choice in the practice of medicine but whether the U.S. FDA should specifically label; these drugs for this use as providing clear and defined benefit given the safety risks.

GlaxoSmithKline Presentations
Dr. David Wheadon, GlaxoSmithKline, provided an introduction of the topic. He indicated COPD is a serious public health issue for the U.S. with considerable unmet needs. Approval of new medicines is important for the appropriate treatment of this debilitating disease. He stated that the data will show that Flovent and Advair provide valuable treatment options for physicians in the management of their patients with COPD.

Dr. Malcolm Johnson reviewed the scientific and clinical rationale for the use of Flovent Diskus and Advair Diskus for the maintenance treatment of COPD.

Dr. James Donohue, of the University of North Carolina, presented a clinician's perspective on the diagnosis and management of the difficult condition of COPD.

Dr. Tushar Shah reviewed the efficacy and safety data from the clinical development programs for Flovent and Advair.

Dr David Wheadon presented the closing statements and directed the questions to the appropriate GSK staff.

FDA Presentations

Dr. Charles Lee presented the safety and efficacy data on Flovent Diskus for COPD. He concluded that for efficacy, there is an effect on the primary efficacy endpoint, change from baseline in FEV1, that is statistically significant, and replicated for fluticasone 500 but is not replicated for fluticasone 250. A small effect was noted in the non-reversible group. Secondary endpoints and patient-reported outcomes showed small differences from the placebo group.

Dr. Lydia Gilbert-McClain, presented Advair Diskus for COPD. Her review determined Advair 250 and Advair 500 both meet the efficacy criteria for combination drugs and the primary endpoints. The efficacy for Advair 250 and Advair 500 was very similar, and almost identical in some evaluations. Numerically the effect size in reversible subjects was greater than the effect size of the non-reversible subjects. However, of clinical importance is the observation that no clear treatment

advantage with Advair was noted for COPD-related quality of life or patient-reported outcomes, COPD symptoms or COPD exacerbations. It is also not clear whether there is a treatment advantage for improvement in dyspnea. There was a clinical significant improvement at endpoint with the TDI instrument for the Advair 500 product, however, there was no clinically significant improvement in dyspnea compared to Advair 500 and its components in the dyspnea domain of the Chronic Disease Questionnaire, a well validated instrument. Taken together, these overall efficacy findings form the basis of FDA's concern regarding the clinical relevance of the FEV1 findings since the efficacy of Advair on airflow limitation did not translate into a clear clinical benefit.

She stated with respect to safety, the adverse events that were seen that were higher in the Advair group compared to the placebo group were similar events that have been previously noted with inhaled corticosteroids -- candidiasis, viral strain infections, hoarseness and dysphonia with both Advair products, and in the case of Advair 500 a higher incidence of upper respiratory tract infections. Again, no adrenal insufficiency was observed in these two studies but bear in mind that this method of testing for adrenal insufficiency might not be able to determine subtle changes in adrenal function. Finally, the studies were not designed, nor were they of significant duration, to evaluate bone mineral density or ocular effects.

Dr. Mary Purucker provided the summary and issues for the committee for discussion.
With regard to product efficacy, she requested discussion of the patient population with regard to the generalizability of the findings to the COPD population as a whole. She requested the committee consider the degree of reversibility and the presence of chronic bronchitis. She reminded the committee that the proposed indication is for long-term twice-daily maintenance treatment of COPD, including chronic bronchitis and emphysema. She indicated FDA would like to hear discussion of the primary endpoint, change from baseline in FEV1, with regard to its clinical relevance to the treatment of COPD. She also requested the committee consider the safety data and discuss whether the data are sufficient with regard to the potential long-term impact on bone or other relevant systemic corticosteroid safety endpoints.

Open Public Hearing had no requests in advance and no one asked to speak when an opportunity was offered.

POINTS FOR DISCUSSION AND QUESTIONS

- Please discuss the patient population studied in clinical trials FLTA3025, SCFA3006, and SCFA3007 with regard to how typical or “representative” they are of US COPD patients in general, and how this would or would not impact on the generalizability of the results of these trials to all COPD patients.

    - **Concern that asthmatics are not al all representative of the COPD population - they are younger and usually have less additional issues to deal with**
    - **They did use a population that had chronic bronchitis and that is a sub-population of COPD therefore it is not fully representative of COPD**

- Please discuss the clinical relevance for the COPD population of the primary endpoint “change from baseline in [pre-dose] FEV_1 over 24 weeks” and the resultant primary efficacy data. .

    - **FEV_1 alone is not sufficient to be a clinical endpoint**
    - **Must consider the risk to benefit ratio to determine if the risk of therapy benefits the patient**
    - **The change in FEV_1 was not associated with a consistent reduction in symptoms as would be expected**

- Please discuss the sufficiency of the safety database to support the use of these products for the long-term, maintenance treatment of COPD.

  - **There is not enough data to support long term use**

QUESTIONS:

1. A. Do the data provide sufficient evidence of efficacy of Flovent Diskus at a dose of 250 mcg twice daily for the for the treatment of chronic obstructive bronchitis?

YES - 2 **NO - 6** **ABSTAIN - 1**

- **There is concern about labeling issues.**
- **There is need for long term maintenance therapy data is needed for mortality or decline in rate of FEV_1**
- **Concern over the lack of reproducibility**
- **Substantive efficacy has not been shown**

B. Do the data provide sufficient evidence of efficacy of Flovent Diskus at a dose of 500 mcg twice daily for the for the treatment of chronic obstructive bronchitis?

YES - 7 **NO - 1** **ABSTAIN - 1**

- **Data shows this dose has efficacy**
- **Desire to see symptom related improvement**
- **Concern over lack of clinical benefits as measured by secondary endpoints**

2. Do the data provide sufficient evidence of efficacy of Advair Diskus (at a dose of 250/50 mcg twice daily, 500/50 mcg twice daily or both) for the treatment of chronic obstructive bronchitis?

YES - 7 **NO - 1** **ABSTAIN - 1**

- **"Long Term" use should be excluded from the labeling**
- **There is sufficient evidence of efficacy**

3 Do the data provide sufficient evidence of safety of Flovent Diskus for the treatment of chronic obstructive bronchitis?

YES - 3 **NO - 5** **ABSTAIN - 1**

- **There is very limited data to use for evaluation of safety in long term use**
- **Concerns of ocular manifestations and bone mass decrease**
- **Population of COPD patients may be more vulnerable to adverse effects than what might occur in asthmatics**
- **Concern over the large number of dropouts**
- **Population studies is much younger than COPD population**

4. Do the data provide sufficient evidence of safety of Advair Diskus for the treatment of chronic obstructive bronchitis?

YES - 4 **NO - 4** **ABSTAIN - 1**

- **Remove "Long Term" and replace with "treatment"**
- **Concerns of ocular manifestations and bone mass decrease**
- **Population of COPD patients may be more vulnerable to adverse effects than what might occur in asthmatics**
- **Safety has only been established for short term treatment**

Advair Diskus and Flovent Diskus for Long-term, Maintenance Treatment of COPD

6. Do you recommend approval of Flovent Diskus for the indication of "long-term, twice-daily maintenance treatment of COPD (including emphysema and chronic bronchitis)"?

YES - 5 **NO - 3** **ABSTAIN - 1**

If Yes:

- At both doses or only one dose?
  - **Only at the 500mcg dose**
- Are there any labeling restrictions or changes needed?
  - **Need very stringent labeling restrictions regarding the difference between COPD and chronic obstructive bronchitis**
  - **Need very specific language on the duration of therapy**
  -
- Are there any phase 4 studies you would recommend?
  - **Require long term monitoring of patients with regard to ocular and bone manifestations**
  - **Require a Phase IV dose escalation study**

If No, what safety and/or efficacy data would the sponsor need to provide to allow for approval?

- **Need to show better effectiveness and provide more long term data**
- **Need the design of very specific and timely Phase IV clinical trials**

6. Do you recommend approval of Advair Diskus for the indication of "long-term, twice-daily maintenance treatment of COPD (including emphysema and chronic bronchitis)"?

YES - 6 **NO - 2** **ABSTAIN - 1**

If Yes:

- At both doses or only one dose?
  - **Both doses**

- Are there any labeling restrictions or changes needed?
    - **Need very stringent labeling restrictions regarding the difference between COPD and chronic obstructive bronchitis**
    - **Need very specific language on the duration of therapy**
- Are there any phase 4 studies you would recommend?
    - **Should require a dose escalation study**

If No, what safety and/or efficacy data would the sponsor need to provide to allow for approval?

- **The relatively modest effect carries with it all the toxicity and safety concerns**