

Airee, Hans N

**From:** Wilson, Lorna C  
**Sent:** Thursday, February 28, 2002 10:01 AM  
**To:** Palmer, James BD; Yamada, Tachi (Notes); Gustafson, Andy N; Rickard, Kathy; Baker, Darrell; Jose, Simon A; Elder, Dave R (US Marketing); Abdalla, Joseph; Jones, C. Elaine; Bohinski, Robert J; Watson, Dawn; House, Karen W; Dorinsky, Paul M; Gerding, Tom A; Sykes, Andy P; Kunka, Bob L; Hackett, Charles P; Airee, Hans N; Edin, Heather M; Soriano, Joan B; House, Karen W; Knobil, Kate; Davis, Kourtney J; Gill, Louise K; Frith, Lucy; James, Mark H; Riebe, Michael T; Clay, Michelle M; Sharma, Raj K; Ho, Shu-Yen Y; Taylor, Stephen W; Yancey, Steve; Davis, Suzanne L; Crim, Courtney; Shrewsbury, Steve B; Ferrell, Joy E; Brannick, Lesley Y (Notes); Wheadon, David E (Notes); Hull, Stan; Skolsky, Steve D; Boyko, David A; Traber, Peter G (Notes); Rockhold, Frank W (Notes); Gibbs, Trevor G; Cree, Fiona (Notes); Pyke, Stephen D; Shah, Tushar P; Hardy, Michele M; Goodwin, Annette G; Rogenes, Paula R; Salyer, Mark W; Reisner, Colin; Devoy, Mike  
**Cc:** Cass, Malcolm; Fitzgerald, Kevin C; Baitinger, Leslie A; Schoaf, Lynne  
**Subject:** ADVAIR DISKUS SUPPLEMENT FOR INITIAL MAINTENANCE THERAPY - NOT APPROVABLE

This supplement to Advair Diskus was submitted on April 27, 2001 and a Not Approvable letter was received late yesterday (letter attached below).

This supplement requested a revision to the Dosage and Administration section of the package insert (see wording below) to provide guidance on the recommendations for the starting dose of Advair Diskus for patients with uncontrolled asthma on SABA only and sought to delete the statement *whose disease severity warrants treatment with 2 maintenance therapies*.

**Current wording:**

For patients who are not currently on an inhaled corticosteroid, whose disease severity warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid maintenance therapy, the recommended starting dose is ADVAIR DISKUS 100/50 twice daily.

**Proposed wording:**

For patients who are currently taking short-acting beta<sub>2</sub>-agonists alone or for patients currently taking non-corticosteroid maintenance therapy, the recommended starting dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily.

**Clinical Studies:**

To support the proposed labeling change, data were provided from five clinical studies which included patients on short-acting beta<sub>2</sub>-agonists alone. One 12-week pivotal clinical study (SAS30017) was conducted in adult and adolescent subjects with persistent asthma that was uncontrolled on short-acting beta<sub>2</sub>-agonists alone. Four supporting studies were also included, including two replicate **DISKUS** studies (SAS40020 and SAS40021) conducted in subjects ≥15 years with asthma uncontrolled on short-acting beta<sub>2</sub>-agonists alone. Two additional supporting studies (SAS30001 and SAS30003) were

conducted which evaluated the combination product delivered by hydrofluoroalkane propellant metered dose inhaler (HFA MDI). The SAS30001 study enrolled patients on short-acting beta2-agonists alone, while SAS30003 included a subset of patients on short-acting beta2-agonists alone.

In the pivotal clinical study (SAS30017) Advair Diskus won on two prespecified primary efficacy endpoints:

- Mean change from baseline in morning pre-dose FEV1 at endpoint for the **DISKUS combination product compared to salmeterol DISKUS**.
- Area under the serial FEV1 curve at Treatment Week 12 relative to Treatment Day 1 baseline for the **DISKUS combination product compared to fluticasone propionate DISKUS**.
- However, for pre-dose FEV1 fluticasone did not achieve significance.

Asthma exacerbations and withdrawals due to worsening asthma were numerically higher, but not statistically significant, across all studies.

#### **FDA Review Comments (in total)**

*We do not believe that you have provided sufficient evidence of efficacy to support this broadened indication for Advair Diskus. Notably, clinical trial SAS30017 failed to demonstrate the superiority of the combination product Advair Diskus to the single component fluticasone propionate using the protocol-specified analysis. In addition, this supplement did not provide adequate assurance of the relative safety of the combination product compared to the single component fluticasone for the proposed population. Withdrawals due to asthma exacerbation and withdrawals due to worsening asthma (clinical and stability-specified) were higher among subjects treated with the combination product compared to the single component fluticasone. In order for this application to be approved, you must provide substantive efficacy and safety data supporting that this specific population uniquely benefits from the combination product in comparison to the individual moieties and that this benefit is not outweighed by any added risks.*

#### **Regulatory Assessment**

While this is disappointing, it is not unexpected. While we won on the prespecified endpoints, it was always a concern that the FDA would require statistical significance for both primary endpoints for both chemical entities. In addition, the FDA raised safety concerns of the combination product versus fluticasone alone for the proposed population. The implication that can be read from this is that the FDA believes that certain patients can be controlled on fluticasone alone.

#### **Next Steps**

There appears to be no additional substantive efficacy and safety data to respond to FDA's comments, however, a recommendation to either amend or withdraw the application will be discussed with key stakeholders in the next few days.



FAX.PDF