

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-658

OFFICE DIRECTOR MEMO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



DIRECTOR'S DECISIONAL MEMORANDUM

Date: Thursday, October 21, 2004
NDA: 21-658
Sponsor: Aventis.
Proprietary Name: Alvesco (ciclesonide) Inhalation Aerosol
Author: Robert J. Meyer, MD, Director, ODE II

Introduction: This is the first cycle for this new molecular entity with a PDUFA due date of October 23, 2004 and the action planned is an approvable action. I have read and substantially concur with Dr. Chowdhury's summary memorandum. Therefore, this signatory memorandum will only be brief, with the full Office Director's memo to be written at the time of approval.

This is the first new inhaled corticosteroid moiety to be submitted to the agency since 1994. It is a pro-drug that is converted in the serum and presumably in the lungs by esterases to the active metabolite – RM1. The latter has an in vitro relative potency to dexamethasone of approximately 12 fold, compared to 18 fold with fluticasone, for example.

The product was originally under development by Altana/Byk Gulden, but the latter stages of development were all done by Aventis (including the phase 3 trials). Unfortunately for the sponsor, despite advice to the contrary, the sponsor did a fairly parsimonious phase 3 that placed most of the emphasis on once-daily dosing, and they failed ~~to~~ studied to show convincing efficacy. This includes the entire pediatric program. They did not include the same nominal daily dose as BID and QD in any single trial. Further, in the studies of more "moderate to severe" asthma (based on prior therapy), the sponsor could not show efficacy for patients who came into the study without prior corticosteroid therapy. This status (prior therapy of corticosteroids or not) was properly a stratification factor at randomization and so the post-hoc analysis of the outcome by these strata is warranted. Ciclesonide is an effective corticosteroid pharmacologically, but the sponsor has failed to demonstrate an appropriate and effective dose and dosing regimen for important segments of the asthma spectrum and for patients below the age of 12 years.

b(4)

b(5)

Therefore, we are taking an approvable action and requiring more studies to establish the correct dose and dosing intervals for Alvesco, particularly in children and in patients not on previous inhaled corticosteroids. Note that there was one foreign inspection site (in the UK) that is scheduled for the morning of the action date. Since the issues in the AE letter are substantive and may take months to years to resolve, we will not wait for any verbal (and certainly not any official) word on the inspection prior to the action, but rather cite the need for an acceptable site inspection prior to approval in the action letter.

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
10/21/04 10:20:52 AM
MEDICAL OFFICER