

Medical Officer's Review of IND 53,391  
Ophthalmology Consult

**IND:** 53,391  
**Ophthalmology Consult**

**Submission Date:** August 21, 2003  
**Received Date:** August 21, 2003

**Review Date:** August 28, 2003

**Sponsor:**

Aventis Pharmaceuticals  
PO Box 6800  
Bridgewater, NJ 08807  
Daniel M. Bollag, PhD, (908) 304-6431

**Drug:**

Ciclesonide

**Pharmacological Category:**

Corticosteroid

**Dosage Form and  
Route of Administration:**

Metered Dose Inhaler

**Proposed Indication:**

Moderate to severe persistent asthma

**Planned Clinical Study:**

XRP 1526B-3027: A multi-center, multinational, randomized, double-blind, parallel group study of the effects of ciclesonide HFA-MDI 640 µg/day and beclomethasone HFA-MDI 640 µg/day on lens opacification in adult subjects with moderate to severe persistent asthma.

**Principal Investigator:**

None specified.

**Reviewer's comments:** *Curriculum vitae and Form 1572 for principal and additional investigators should be submitted prior to the start of the study.*

**Background:**

On June 2, 2003, members of the Divisions of Pulmonary and Allergy Drug Products and Ophthalmic Drug Products met with the sponsor, Aventis Pharmaceuticals, to discuss issues pertaining to ophthalmic adverse events resulting from 2 completed studies. Specifically, in 2 Aventis trials, new cataracts were more frequently found in patients given ciclesonide than in patients given two active controls or placebo. Due to procedural inconsistencies in the 2 studies, it was unclear whether the association was real. The sponsor agreed to study the veracity of this apparent safety signal with an additional trial. The Division of Pulmonary and Allergy Drug Products requests consultation for the proposed protocol.

**Proposed Clinical Protocol XRP1526B-3027:****Study Objective:**

The primary objective is to demonstrate the non-inferiority of ciclesonide compared to beclomethasone in the occurrence of a Class 1 lens event outcome for nuclear (NO), cortical (C), or posterior subcapsular (P) lens opacification within 12 months.

**Subjects:** Approximately 1200 subjects (600 each arm) of any race and either sex with a history of moderate to severe persistent asthma will be randomized and treated with either ciclesonide or beclomethasone. The expected number of randomized subjects per site is 6 to 20.

**Key Inclusion Criteria:**

1. Male and female subjects > 18 years of age, of any race
2. History of at least 2 months moderate to severe asthma
3. At screening, FEV<sub>1</sub> must be  $\geq 40\%$  and  $\leq 85\%$  of predicted
4. Documented use of inhaled corticosteroid therapy at any dose for at least 1 month prior to screening
5. Non-smoker at least 1 year and less than 10 pack year history if previous smoker

**Key Exclusion Criteria:**

1. History of prior cataract surgery in either eye
2. Evidence of congenital cortical cataract
3. Inability to grade lens opacities in either eye with LOCS III at baseline slit lamp exam
4. Inability to dilate pupils to at least 6 mm
5. Nuclear opalescence with a LOCS III  $\geq 4$  in either eye at baseline
6. Cortical lens opacities with a LOCS III  $\geq 3$  in either eye at baseline
7. Posterior subcapsular lens opacities with a LOCS III  $\geq 2$  in either eye at baseline
8. Elevated IOP requiring treatment
9. BCVA less than 74 letters in either eye at baseline
10. Pregnant or lactating females or those with positive screening pregnancy test
11. More than 1 in-patient hospitalization in past year for asthma exacerbation

12. More than 12 bursts of oral steroids except for inhaled corticosteroids for any condition. Topical steroids with a mild potency per the Stoughton-Cornell Scale or European Guideline for levels of corticosteroid activity are allowed.
13. Chronic condition that is likely to require treatment with oral or systemic corticosteroids other than asthma.

**Reviewer comments:** *Recommend additional exclusion criteria:*

1. *Topical ocular steroid treatment within 3 months*
2. *Chronic or recurrent inflammatory eye disease in either eye*

**Study Description:** This is a multi-center, multinational, randomized (1:1), double-blind, active-controlled parallel group study of the effects of ciclesonide HFA-MDI 640 µg/day and beclomethasone HFA-MDI 640 µg/day (4 actuations bid; 80 µg/actuation ex-actuator) on lens opacification in adult subjects with moderate to severe persistent asthma. The randomization will be stratified by geographic region and subject age group (2:1 overall ratio of ≥40 years to <40 years). Subject compliance will be monitored by daily diary entries of medication usage.

The study consists of a 1-14 day screening phase during which subject eligibility will be determined, followed by a 12-month double-blind treatment phase. Lens opacification will be evaluated by slit lamp exam (after pupillary dilation to at least 6 mm) before randomization and after 4 months, 8 months, and 12 months of treatment using the Lens Opacities Classification System III (LOCS III) system. Best-corrected visual acuity (BCVA) and intraocular pressure (IOP) will be measured at each eye exam visit.

An Independent Data Monitoring Committee (IDMC) will monitor safety throughout the double-blind treatment phase and conduct one interim analysis of 4-month eye examination data when at least 50% of all subjects have completed their 4-month eye examination. If the IDMC feels that certain action is required, then the nominal significance level for the assessment of non-inferiority will be 0.001 at this interim analysis, and 0.049 at the final analysis. A one-sided 99.95% confidence interval will be constructed for the ratio of the life-table estimates of the four-month event rates for non-inferiority, and the non-inferiority bound to be used for comparison will be 2. The study will not be stopped early for non-inferiority.

**Reviewer comment:** *Any time points intended for data analysis by the IDMC, including safety monitoring, should be specified in advance and proper statistical adjustments should be made accordingly.*

**Study Schedule:**

Visit# (E=eye)	V1	V1E		V2	V3	V4	V4E	V5	V6	V6E	V7	V8E	V8
Time point (Day, Month)	1-14 Days		Randomize	Day 1	M2 +/- 7d	M4 +/- 7d	M4 +/- 14d	M6 +/- 7d	M8 +/- 7d	M8 +/- 14d	M10 +/- 7d	M12 +/- 7d <sup>a</sup>	M12 +/- 7d
Manifest refraction		X					X			X		X	
Visual Acuity		X					X			X		X	
IOP		X					X			X		X	
SLE		X					X			X		X	
Informed Consent	X												
Randomization			X										
D/C prior steroids				X									
Medical/Drug Treatment hx	X												
Collect/review diary				X	X	X		X	X		X		X
Collect study drug/perform accountability					X	X		X	X		X		X
Prior and/or concomitant med review	X			X	X	X		X	X		X		X
AE review				X	X	X		X	X		X		X
PFT	X			X	X	X		X	X		X		X
Labs	X					X							X
PE	X					X							X
Dispense diary	X			X	X	X		X	X		X		
Dispense study meds <sup>b</sup>				X	X	X		X	X		X		

<sup>a</sup> Should always be performed prior to Visit 8 even if both visits occur on same day.

<sup>b</sup>Dispense rescue albuterol as needed.

**Reviewer comment:** *Efforts should be made to measure IOP at the same time of day as the baseline visit.*

**Safety and Efficacy Evaluation:**

The sponsor describes the assessment methodology for IOP, visual acuity and LOCS III in an Appendix.

**Reviewer comment:** *The proposed assessment methodology is acceptable.*

The **primary endpoint** is the occurrence of a Class 1 lens event for nuclear (NO), cortical (C) or posterior subcapsular (P) lens opacification within 12 months.

A **Class I lens event** is defined as any of the following events in either eye:

1. Increase from baseline in LOCS III grade of  $\geq 0.5$  NO,  $\geq 0.8$  (C), or  $\geq 0.5$  (P)
2. Cataract surgery

**Secondary endpoints:**

1. Change from baseline to Month 12 in LOCS III grade for NO, C, or P opacity

2. Occurrence within 12 months in either eye of a Class II lens event: increase from baseline in LOCS III grade of  $\geq 0.9$  NO,  $\geq 1.5$  (C), or  $\geq 0.9$  (P)
3. Occurrence within 12 months in either eye of a Class III lens event: increase from baseline in LOCS III grade of  $\geq 2.0$  for any type of opacity (NO, C, P) and a change in LOCS III grade of  $\geq 0.9$  NO,  $\geq 1.5$  (C), or  $\geq 0.9$  (P), or cataract surgery
4. Change from baseline to Month 12 in BCVA
5. Change from baseline to Month 12 in IOP

**Tertiary endpoint:**

Change in post-bronchodilator FEV<sub>1</sub> from baseline to month 12

**Statistical Hypothesis and Methods of Analyses:**

All patients who receive study medication will be considered evaluable for the safety analysis.

The primary analysis population will be the modified intent-to-treat population. This will include all randomized subjects who receive at least one dose of study medication, and meet at least one of the following criteria:

1. A pre-treatment and at least one post-treatment LOCS III measurement, or
2. A post-treatment cataract surgery within 12 months

Assuming an 8% event rate within 12 months for the primary Class I event, about 503 subjects will be required per treatment group to achieve 90% power for non-inferiority based on a one-sided 97.5% CI of the risk ratio. If the event rate is lower than 8% in the control group, then the power of the study is lower than 90%.

The primary analysis for the primary endpoint of the Class I event will be the comparison for non-inferiority between treatment (ciclesonide) and control (beclomethasone) of the proportion of subjects with a Class I event within 12 months. Non-inferiority will be assessed at a significance level of 0.025 (2-sided significance level of 0.05) by comparing the upper bound of the one-sided 97.5% confidence interval of the risk ratio with the non-inferiority bound, NIB. Non-inferiority of ciclesonide versus the control will be demonstrated if the upper bound of the one-sided 97.5% CI is less than the non-inferiority bound. In non-inferiority is demonstrated, then superiority of ciclesonide over control can be subsequently tested by comparing the upper bound of the one-sided 97.5% CI to one without adjusting the level of significance. In order to assess the consistency of the results of the primary analysis approach, the analysis will also be performed for the per protocol population.

**Reviewer comments:** *Acceptable.*

**Informed Consent:** *Not submitted.*

**Problem List/Deficiencies:**

1. Curriculum vitae and Form 1572 for principal and additional investigators should be submitted prior to the start of the study.
2. Recommend additional exclusion criteria:  
Topical ocular steroid treatment within 3 months  
Chronic or recurrent inflammatory eye disease in either eye
3. Any time points intended for data analysis by the IDMC, including safety monitoring, should be specified in advance and proper statistical adjustments should be made accordingly.
4. Efforts should be made to measure IOP at the same time of day as the baseline visit.

**Recommended Regulatory Action:**

It is recommended that the sponsor address the deficiencies and problems noted in this review prior to initiating a study.

Matt Feinsod, M.D.  
Medical Officer

cc: HFD-550/CSO/  
HFD-550/CHEM/  
HFD-550/PHARM/  
HFD-550/Dep Div Dir/Chambers

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Matthew Feinsod  
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Wiley Chambers  
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Medical Officer's Review of IND 53,391  
Ophthalmology Consult

**IND:** 53,391  
**Ophthalmology Consult**

**Submission Date:** June 29, 2005  
**Received Date:** June 30, 2005  
**Review Date:** September 26, 2005

**Sponsor:** Sanofi Aventis  
200 Crossing Boulevard  
PO Box 6890  
Bridgewater, NJ 08807-0890  
Daniel M. Bollag, PhD, (908) 304-6431

**Drug:** Ciclesonide

**Pharmacological Category:** Corticosteroid

**Dosage Form and Route of Administration:** Metered Dose Inhaler

**Proposed Indication:** Moderate to severe persistent asthma

**Planned Clinical Study:** XRP 1526B-3027: A multi-center, multinational, randomized, double-blind, parallel group study of the effects of ciclesonide HFA-MDI 640 µg/day and beclomethasone HFA-MDI 640 µg/day on lens opacification in adult subjects with moderate to severe persistent asthma.

**Background:**  
On June 2, 2003, members of the Divisions of Pulmonary and Allergy Drug Products and Ophthalmic Drug Products met with the sponsor, Aventis Pharmaceuticals, to discuss issues pertaining to ophthalmic adverse events resulting from 2 completed studies. Specifically, in 2 Aventis trials, new cataracts were more frequently found in patients given ciclesonide than in patients given two active controls or placebo. Due to procedural inconsistencies in the 2 studies, it was unclear whether the association was real. The sponsor agreed to study the veracity of this apparent safety signal with an additional trial.

**Submitted:**  
With this correspondence, Aventis, a member of the sanofi-aventis group, is submitting a change in protocol XRP1526B/3027 (Amendment #3), dated June 28, 2005. In this protocol amendment, Aventis is making an adjustment for the non-inferiority bound for event rates that are ≥ 30%.

Justification of changes:

Study title: *A Multi-Center, Multinational, Randomized, Double-Blind, Parallel Group Study of the Effects of Ciclesonide HFA-MDI 640 ug/Day and Beclomethasone HFA-MDI 640 ug/Day on Lens Opacification in Adult Subjects with Moderate to Severe Persistent Asthma.*

This study was designed to evaluate the potential for lens opacification occurring during one year of administration of ciclesonide MDI compared to beclomethasone HFA-MDI. To achieve this objective, a standardized system for rating lens opacity (LOCS III) was selected, and a system for classifying events (Class I, II, and III) was developed in consultation with the FDA.

At the time the protocol was designed, event rates for the primary endpoint (Class I events) were estimated to be below 10%. As the study is nearing completion, a review of the blinded data reveals a primary endpoint event rate that exceeds 30%. In order to retain adequate power to assess non-inferiority at event rates above 30%, Aventis is amending the study protocol to allow for a constant value of the non-inferiority bound of 1.333 for event rates  $\geq 30\%$ .

**Reviewer's Comments:** *Disagree. As demonstrated by the tables provided, there is sufficient power to provide an adequate comparison to the control group with the 700 patients per arm that have already been enrolled. The increased event rate suggests more of a concern with the potential development of cataracts, and the non-inferiority bound should be set at no greater than 1.1.*

**Recommended Regulatory Action:**

1. It is recommended that the sponsor's proposal not be accepted and that if the non-inferiority bound is increased, it should not be planned to be increased greater than 1.1.
2. Six hundred (600) evaluable patients per arm should be adequate to provide a sufficient estimate of the cataract rate.

Wiley A. Chambers, M.D.  
Deputy Division Director, Ophthalmology

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**MEDICAL OFFICER REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA 21-658	<b>TRADE NAME:</b> Alvesco
<b>APPLICANT/SPONSOR:</b> Aventis	<b>FORMULATION:</b> Ciclesonide
<b>MEDICAL OFFICER:</b> Carol H. Bosken, MD	HFA Aerosol
<b>TEAM LEADER:</b> Lydia Gilbert-McClain, MD	<b>CATEGORY:</b> Corticosteroid
<b>DUE DATE:</b> N/A	<b>ROUTE:</b> Oral inhalation

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Submission Type &amp; Comments</u>
February 1, 2005	February 2, 2005	N (000) C	Sponsor Query

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
February 5, 2004	NDA 21-658	Original NDA

**REVIEW:** This submission is a request to review the sponsor's request for clarification of the FDA expectations for approval of Alvesco in \_\_\_\_\_ years of age. Aventis is planning two additional studies in adults and adolescents: one (#3030) 12-week study on patients who previously received inhaled corticosteroids (ICS) comparing 160 mcg Alvesco QD to 80 mcg BID, and placebo; one (#3031) 16-week study in patients not previous on ICS comparing 160 mcg Alvesco QD to 80 mcg BID and Alvesco 80 mcg BID for 4 weeks followed by Alvesco 160 mcg OD for 12 weeks. The sponsor wants verification that we will accept the integrated analysis of the \_\_\_\_\_ previously submitted with the original \_\_\_\_\_

b(4)

\_\_\_\_\_. Furthermore the sponsor believes that the 80 mcg dose has already been demonstrated to be the lowest effective dose because the \_\_\_\_\_ mcg once daily was ineffective in studies 341 and 342.

**COMMENTS:** See attached question and answer

Question and Answer

b(4)

**Question:** If the proposed additional clinical studies in adults and adolescents confirm the efficacy of Alvesco, does the FDA agree that the available data can support a claim in \_\_\_\_\_ years old?

**Answer:** No, we do not agree. The additional studies #3030 and #3031 may provide adequate information to evaluate the safety of ciclesonide 160 mg daily administered as 80 mcg twice daily or 160 mcg once daily in adults. However, the studies do not address the efficacy of the 80 mcg daily dose. \_\_\_\_\_

b(4)

\_\_\_\_\_ The Division maintains that efficacy of the 80 mcg daily dose has not been established in adults since efficacy was demonstrated in only one study (study # 322).

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Lydia McClain  
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population) in adult and adolescent patients with mild to moderate asthma is sufficient for such dosing recommendations. Does the FDA concur?

*Answer 4: We concur that an inhaled corticosteroid should be effective in subjects with asthma regardless of their prior therapy. We note, however, that the efficacy of ciclesonide in adult asthmatic subjects not previously treated with ICS was not demonstrated at any dose, in the two trials in which this analysis was performed. Therefore, the study population must be large enough to support efficacy in the sub-populations defined by prior corticosteroid use so that the label can contain recommendations for each patient group. The resulting label will then conform to the format of all labels of inhaled corticosteroids approved for treatment of asthma in the United States.*

Question 5. If the data demonstrate that a once-daily regimen is superior to placebo and similar to a twice-daily regimen, Aventis believes that the proposed clinical trial will support \_\_\_\_\_

*Answer 5: In principle, efficacy in subjects \_\_\_\_\_ years of age may be extrapolated from the*

**b(4)**

Question 6: If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, Aventis believes that the proposed clinical study will support twice-daily dosing recommendations in \_\_\_\_\_ patients. Does the FDA concur?

*Answer 6: Refer to the answer to question 5.*

*Additional FDA comment: Be aware that depending on the final outcome of the proposed clinical study (ies), the dose selection chosen for the pediatric growth study (#343) may not be appropriate and the growth study may need to be repeated.*

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Lydia McClain  
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MEDICAL OFFICER

NDA # 21-658, Ciclesonide (Alvesco™)

## Memo to File

DATE: September 30, 2004  
FROM: Carol H. Bosken, Medical Officer  
THROUGH: Lydia Gilbert-McClain, Team Leader  
SUBJECT: Amendment to Primary Medical Review of NDA 21-658

It was noted that Tables 6 and 7 on pages 39 and 40 of the Medical Officer's primary review did not render correctly into PDF. This amendment to the submission contains pages 39 and 40 with the corrected Tables.

In the NDA ISS the applicant has summarized the data in several ways. Adverse events are presented for the combined 12-week adult studies in subjects with mild to severe asthma, including the 12-week PD study (321, 322, 323/324, and 102). Separate summaries are presented for the 12-week oral prednisone reducing study (325). The 1-year safety studies are presented in three combinations: 1 summary present the data for study 323/324, one summary presents the data for study 326, and one study presents the data for the combination of 323/324 and 326. For the current review, only the combined data will be presented in tabular form.

One of the subjects enrolled in study 3411t died while taking study medication. A detailed autopsy report was submitted to the ciclesonide IND as a follow-up of a serious and unexpected adverse event, and this was also reviewed (*IND 53391, series 216, stamp date May 14, 2004*).

## 1.1. Description of Patient Exposure

### 1.1.1. Adult and Adolescent Subjects

An overall summary of the experience with ciclesonide treatment in the adolescent/adult population is shown in Table 6. There were 352 subjects treated for  $\geq 6$  months and 313 who were treated for  $\geq 12$  months.

**Table 1. Total Exposure of Adults to Ciclesonide**

Type of study	Study, or studies integrated	Number of subjects treated with ciclesonide				Total
		$\leq 12$ weeks <sup>a</sup>	>12 weeks <sup>a</sup> to <6 months <sup>b</sup>	$\geq 6$ months <sup>b</sup>	$\geq 12$ months <sup>c</sup>	
Controlled 12-week efficacy and safety studies	321, 322, 323/324, 102	1069	33	0	0	1102
Controlled 12-week study on effectiveness of reducing oral corticosteroid use	325	92	4	0	0	96
Controlled 4-week PD safety study on HPA-axis function	103	24	0	0	0	24
Controlled 1-year safety study	323/324LT	31	18	148	129	197
Uncontrolled 1-year safety study	326	27	5	194	175	226
All studies (total exposure)		967 <sup>d</sup>	88 <sup>d</sup>	352 <sup>d</sup>	313 <sup>d</sup>	1407

<sup>a</sup> 90 days; <sup>b</sup> 176 days; <sup>c</sup> 351 days

*\*(Source: applicant's table 7 [update/summary] 2.7.4 clinical efficacy. pg 36.)*

The safety population of the 12-week adult trials (321, 322, 323/324, and 102) was composed of 1102 subjects who were treated with ciclesonide 80, 160, 320 mcg QD or 160 or 320 mcg BID for a mean of 76.5 (median of 84) days. For comparison, 429 subjects were treated with placebo for a mean of 63.0 (median of 83) days and 179 subjects were treated with fluticasone 880 mcg a day for a mean of 76.2 (median of 84)

days. The majority were treated for more than 78 days (63.6, 84.4, 84.9, 83.4, 84.1, and 82.1% in the placebo, ciclesonide-80, ciclesonide-160, ciclesonide-320, ciclesonide-640, and fluticasone-880 groups respectively).

In the OCS reducing study (325) the mean exposure of the 96 subjects treated with ciclesonide (640 or 1280 mcg/day) was 79.8 days (median of 84). In the 1-year safety follow-up studies (326, 323/324lt) subjects were treated with varying doses of ciclesonide (80 – 320 mcg / day) for a mean of 296.1 (median of 364) days.

### 1.1.2. Pediatric Population

An overall summary of the experience with ciclesonide treatment in the pediatric population is shown in Table 7. There were 370 subjects treated for  $\geq 6$  months and 328 who were treated for  $\geq 12$  months.

**Table 2. Total Exposure to Ciclesonide for Subjects 4 – 11 Years of Age\***

Type of study	Study, or studies integrated	Number of subjects treated with ciclesonide				Total
		$\leq 12$ weeks <sup>a</sup>	>12 weeks <sup>a</sup> to <6 months <sup>b</sup>	$\geq 6$ months <sup>b</sup>	$\geq 12$ months <sup>c</sup>	
Aventis controlled 12-week efficacy and safety studies	341, 342	689	79	0	0	768
Aventis controlled 1-year safety studies	341LT, 342LT, 344	45	37	361	321	443
Altana controlled PD safety studies on lower-leg growth velocity	FK1 201, M1-203	48	0	0	0	48
<b>Total</b>		<b>573<sup>d</sup></b>	<b>150<sup>d</sup></b>	<b>370</b>	<b>328</b>	<b>1093</b>

<sup>a</sup> 91 days; <sup>b</sup> 176 days; <sup>c</sup> 351 days

<sup>d</sup> All studies = number of subjects by exposure duration category counting total ciclesonide exposure in one or more studies (i.e., from participation in a 12-week study followed by participation in the corresponding 1-year study). The rows above refer to exposure in type of study. Hence the numbers in the columns do not add up to the numbers in the

\*(Source: applicant's table 4 [update/summary/2.7.4b/clinical/safety. pg 27])

The safety population of the 12-week pediatric trials (341 and 342) was composed of 768 subjects who were treated with ciclesonide 40, 80, or 160 mcg QD for a mean of 78.6 (median of 84). For comparison, 257 subjects were treated with placebo for a mean of 75.7 (median of 84) days. The majority were treated for more than 78 days (80.5, 83.2, 85.4, and 88.2% in the placebo, ciclesonide-40, ciclesonide-80, and ciclesonide-160 groups respectively). In the 1-year safety follow-up studies (341, 342, and 344) subjects were treated with varying doses of ciclesonide (80 – 160 mcg/day) for a mean of 301.8 (median of 364).

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Carol Bosken  
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MEDICAL OFFICER

## MEDICAL OFFICER REVIEW

### Division Of Pulmonary and Allergy Drug Products (HFD-570)

**APPLICATION:** NDA # 21-658      **TRADE NAME:** Alvesco™  
**APPLICANT:** Aventis      **USAN NAME:** Ciclesonide  
**MEDICAL OFFICER:** Carol H. Bosken, M. D.  
**TEAM LEADER:** Lydia I. Gilbert-McClain, M.D.      **CATEGORY:** Corticosteroid  
**DUE DATE:** October 22, 2004      **ROUTE:** Oral inhalation

#### ELECTRONIC SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>Submission</u>	<u>Comments</u>
December 22, 2003	N(000)	Original NDA
February 5, 2004	N(000), BZ	Amended NDA (links corrected)
March 22, 2004	N(000), C	Plans to _____
April 26, 2004	N(000), SU	120-Day Safety Update
April 26, 2004	N(000), BM	Response to FDA query RE: HPA-axis testing
May 27, 2004	N(000), PB	Request for waiver for children < 6 months of age
August 4, 2004	N(000), BZ	HPA-axis re-analysis

#### RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
April 10, 1998	IND 53,391	Original ciclesonide IND
May 14, 2004	IND 53,391 (s_216)	Follow-up serious adverse event (death) report

**REVIEW SUMMARY:** This NDA is for ciclesonide (Alvesco™), for the maintenance therapy of asthma in subjects —/years of age and older. Ciclesonide is a pro-corticosteroid and a new molecular entity. The inactive parent compound is poorly absorbed in the gastrointestinal tract but it is metabolized to an active form in the lung. On this basis, the applicant suggests that HPA-axis suppression is less with ciclesonide than with other corticosteroids.

In two 12-week efficacy trials (Study 321 and 322, n=1015) adult and adolescent ≥ 12 years of age who had mild to moderate persistent asthma were treated with 80, 160, and 320 mcg ciclesonide in a single daily dose. Only the 320 mcg dose was effective in both trials. In addition, the 320 mcg dose was only effective in subjects who were being treated with inhaled corticosteroids (ICS) at the time of enrollment.

In a single 12-week efficacy trial (Study 323/324, n=531) adult and adolescents ≥ 12 years of age with moderate to severe asthma were treated with 160 or 320 mcg ciclesonide BID. All of the subjects were being treated with ICS prior to enrollment. Both the 160 and 320 mcg BID doses improved pulmonary function and asthma symptom scores. One additional 12-week efficacy trial (Study 325, n=141) was conducted in adult and adolescents ≥ 12 years of age who required treatment with oral corticosteroids. In these subjects, ciclesonide 320 or 640 mcg BID was effective in reducing the oral corticosteroid requirement.

In two 12-week efficacy trials (Study 341 and 342, n= 1031) children 4 – 11 years of age with mild to severe persistent asthma were treated with ciclesonide 40, 80, and 160 mcg daily. In none of the tested doses was there a reproducible improvement in pulmonary function or symptoms.

The spectrum of adverse events was similar to that seen during treatment with other ICS. The incidence of oral candidiasis was low, but did occur at higher doses. Similarly, HPA-axis suppression was infrequent, but did occur at higher doses. No conclusions can be drawn as to the relative safety comparing ciclesonide to other ICS because they were not tested at equipotent doses.

b(4)

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**OUTSTANDING ISSUES:** In study 323/324 an excess of lenticular opacities was seen in the ciclesonide-treated subjects, and the frequency of the abnormalities were dose-related. The incidence was less in the 1-year follow-up study, and it was not higher than the incidence seen in QVAR treated subjects. However, none of the submitted trials was designed to directly test the hypothesis that ciclesonide promotes the development of cataracts to a degree that is not seen during treatment with other ICS. The applicant is currently conducting a 1-year study to compare the development of cataracts in adult and adolescent treated with ciclesonide to subjects treated with QVAR. It is anticipated that the study report will be completed early in 2005.

**RECOMMENDED REGULATORY ACTION**

NDA/SUPPLEMENTS:	<input type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE
	<input checked="" type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE
OTHER ACTION:	<input type="checkbox"/>	<input type="checkbox"/> NOT APPROVABLE

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Description</b>
AE	Adverse Event
AQLQ	Asthma Quality of Life Questionnaire
ALT	Alanine amino transferase
AMP	Adenosineonophosphate
AUC	Area Under the Curve
CI	Confidence Interval
CMC	Chemistry Manufacturing and Controls
C <sub>max</sub>	Maximum concentration of a drug in the blood after dosing
CYP	Cytochrome P450
DPI	Dry powder inhaler
ERS	European Respiratory Society
FEV <sub>1</sub>	Forced Expired Volume in 1 second
FP	Fluticasone propionate
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
ICS	Inhaled corticosteroids
IOP	Intra-ocular pressure
ITT	Intention to Treat
IV	Intravenous
KA	Rate of absorption
L	Liters
LEF	Lowest Effective dose of prednisone required to maintain asthma control.
LOCF	Last observation carried forward
LPS	Lipopolysaccharide
LS	Least Square
MDI	Metered dose inhaler
Meq	Miliequivalent
NAEPP	National Asthma Education and Prevention Program
NO	Nitric Oxide
OCS	Oral corticosteroids
OCT	Oral contraceptive pills
PCA	Predefined Change Abnormal
PD	Pharmacodynamic
PEF	Peak Expiratory Flow

Executive Summary

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PK	Pharmacokinetic
PBB	Parts per Billion
RM1, RM9	Metabolites of R-ciclesonide.
RBC	Red Blood Cells
T <sub>max</sub>	Time of maximum concentration of a drug in the blood after dosing.
T <sub>1/2</sub>	The time it takes for the blood level of a drug to reach ½ of its peak level.
WBC	White Blood Cells

Executive Summary

## CLINICAL REVIEW OF NDA # 21-658

### EXECUTIVE SUMMARY

#### 1. RECOMMENDATIONS

##### 1.1. Recommendation on Approvability

Ciclesonide 320 mcg QD (ex-actuator) is recommended for the maintenance treatment of asthma in subjects 12 years of age or older with mild to moderate persistent asthma who have previously been treated with inhaled corticosteroid (ICS) therapy. Ciclesonide 160 mcg BID, or 320 mcg BID (ex-actuator) is recommended for adult and adolescent asthmatics age 12 and above with moderate to severe disease who have been previously treated with ICS. The recommendation is based on the improvement that is seen in pulmonary function, symptoms, and patient reported outcomes compared to treatment with placebo. Adverse events were not more common or severe than those seen after treatment with other inhaled corticosteroids (ICS) except for the possible increased incidence of lenticular opacities.

Ciclesonide 320 mcg BID and — mcg BID (ex-actuator) is recommended for the maintenance treatment of asthma in subjects 12 years of age or older who require maintenance oral corticosteroid (OCS) therapy. The recommendation is based on the significant decrease in OCS requirement compared to placebo treatment.

##### 1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

No phase 4 studies are recommended.

#### 2. SUMMARY OF CLINICAL FINDINGS

##### 2.1. Brief Overview of Clinical Program

Ciclesonide is a new molecular entity. The development program includes CMC evaluations, toxicology studies, and PK and PD studies in addition to the clinical trials. The clinical approval recommendation is based on review of 11 pivotal efficacy and safety and long term safety trials. There were two identical 12-week randomized, double-blind, placebo controlled efficacy trials in subjects 12 years of age and older (n=1015) who had mild-to-moderate asthma. Randomization was stratified on the basis of prior ICS therapy, and treatments included ciclesonide in doses of 80, 160, and 320 mcg once daily as well as placebo. The change in FEV<sub>1</sub> over the 12-week treatment period was the primary outcome measure. There was a single 1-yr, open-label safety follow-up of 226 of the subjects enrolled in these two pivotal trials.

There was one randomized, double-blind, placebo-controlled 12-week efficacy trial in adults with moderate-to-severe asthma, all of whom had been treated with ICS prior to screening (n=528). Ciclesonide in doses of 160 mcg BID and 320 mcg BID were compared to placebo and to fluticasone 440 mcg BID. The primary efficacy outcome was change in FEV<sub>1</sub> over the 12-week treatment period. A single 1-year double-blind safety follow-up study was conducted: Subjects were randomized to receive ciclesonide or QVAR. At enrollment into the follow-up trial, subjects took 320 mcg daily of study medication and then the dose could be lowered at the discretion of the investigator.

A randomized, double-blind, placebo-controlled 12-week study was conducted in subjects with moderate to severe asthma who were dependent on oral corticosteroids (n=141). Subjects were treated with ciclesonide 320 mcg BID, ciclesonide 640 mcg BID, or placebo and the primary outcome measure was the percent reduction in oral prednisone dose.

Two identical 12-week, randomized, double-blind, placebo-controlled trials were conducted in children 4 – 11 years of age with mild-to-severe asthma (n=1043). Randomization was stratified on the basis of prior ICS therapy, and treatments included ciclesonide in doses of 40, 80, and 160 mcg once daily as well as placebo. The change in FEV<sub>1</sub> percent predicted over the 12-week treatment period was the primary outcome measure. There was one 1-yr, randomized, safety follow-up of each of the pivotal trials. There was one additional randomized, 1-year safety evaluation of subjects 4 – 11 years of age with mild-to-severe asthma. In all of the 1-year follow-up trials the subjects were randomized to ciclesonide 160 mcg daily or fluticasone 100 mcg BID. After 2 weeks the dose of either drug could be reduced at the investigator's discretion.

## 2.2. Efficacy

In the two 12-week pivotal trials in adults and adolescents with mild to moderate asthma who had been treated with inhaled corticosteroids prior to enrollment, ciclesonide at a dose of 320 mcg QD was effective in improving pulmonary function. Efficacy was not demonstrated for lower doses or for subjects who had been treated with bronchodilators only prior to enrollment. Some of the secondary outcome measures supported the efficacy of the 320 mcg QD dose. However, the Asthma Quality of Life Questionnaire (AQLQ) showed a meaningful improvement for the 320 mcg QD dose in only one of the trials. The efficacy of the 320 mcg dose was maintained throughout the 12 week trials and the 1-year safety follow-up.

There was a significant response to ciclesonide at 160 mcg BID and 320 mcg BID in adults and adolescents with moderate to severe asthma who had been treated with ICS prior to enrollment. FEV<sub>1</sub> and other measures of asthma control such as asthma symptoms, and the Overall Score of the AQLQ improved with treatment at both doses. Similarly, subjects with moderate to severe asthma who had previously been treated with OCS responded favorably to treatment with ciclesonide 320 mcg BID and 640 mcg BID in that treatment with both doses of ciclesonide resulted in substantial decreases in the requirement for oral corticosteroids.

In children 4 – 11 years of age ciclesonide was not effective in any of the doses tested. There was no consistent improvement in FEV<sub>1</sub>, symptoms or the AQLQ at any of the doses.

### 2.3. Safety

Adverse events (AE) after treatment with ciclesonide were generally mild to moderate in intensity and except for the findings of ocular opacities were similar to AEs seen in other asthma trials with other inhaled corticosteroids. The most common events were respiratory tract abnormalities and infections. Asthma exacerbations were common adverse events, a common cause of withdrawal of subjects from the study, and more common in the placebo-treated subjects. In the placebo-treated adults and adolescents, 17.2% withdrew due to an asthma exacerbation compared with 3.8 to 8.7% of the subjects treated with ciclesonide in the adult pivotal trials. The incidence of oral candidiasis was low with 1.0% of the subjects in the adult and adolescent pivotal trials reporting this AE compared to 0.9% in the placebo subjects. In the pediatric 12-week trials there were only 2 cases of candidiasis reported in the ciclesonide-treated subjects, and in the 1-year pediatric follow-up studies 4 cases (0.9%) were reported. Abnormalities of the Hypothalamic-Pituitary-Adrenal-axis (HPA-axis) were also infrequent. The mean changes in baseline and peak post-cosyntropin stimulation serum cortisol after treatment with ciclesonide were very small and very few subjects changed from normal function at baseline to abnormal after treatment. Ciclesonide did not cause more HPA-axis suppression than fluticasone in these studies, although, the dose tested were not equipotent. The potential for HPA-axis suppression due to ciclesonide relative to fluticasone can not be assessed without a direct comparison between doses that produce an equal degree of bronchodilatation.

Lenticular opacities were detected in adults with moderate to severe asthma after treatment with ciclesonide. For subject who had normal ophthalmologic examinations at baseline, the incidence was 1.0, 3.4, and 8.7% detected after 12 weeks of treatment with placebo, ciclesonide 160 mcg BID and 320 mcg BID, respectively. Cataracts were also detected in the 1-year follow-up studies, but not in an incidence that was higher than the comparator ICS beclomethasone dipropionate (QVAR). None of these studies was designed prospectively to detect cataracts and the final conclusion of this question will have to await the ongoing one-year study designed to evaluate whether treatment with ciclesonide is associated with the development of lenticular opacities. Although less common, cataracts were also detected in the pediatric trials. In the 1 year follow-up trials, 9 (2.3%) of ciclesonide-treated subjects with normal eyes at baseline had cataracts detected after treatment compared to 2 (1.5%) of subjects treated with fluticasone. Considering that asthma therapy may be required for life, it will be important to resolve the issue in both children and adults.

### 2.4. Dosing

For adult and adolescents  $\geq 12$  years of age with mild to moderate asthma who have previously been treated with ICS, a starting dose of ~~—~~ mcg QD can be approved.

b(4)

For adult and adolescents who require OCS treatment, the starting dose is 320 mcg BID. This can be increased to ~~—~~ mcg BID if necessary

**2.5. Special Populations**

Ciclesonide is not recommended for the maintenance treatment of asthma in subjects < 12 years of age. Dose modification is not necessary for older subjects, although testing in this age-group has not been extensive. In subjects with hepatic insufficiency, ciclesonide metabolism may be slower and the lowest possible dose should be used. There is no need for dose adjustment in subjects with renal impairment.

**APPEARS THIS WAY ON ORIGINAL**

## CLINICAL REVIEW

### 1. INTRODUCTION AND BACKGROUND

#### 1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This NDA is submitted in support of Alvesco (R-ciclesonide) HFA-134a Metered Dose Inhaler (MDI), a non-halogenated glucocorticoid for use in the prophylaxis of asthma. Ciclesonide, itself, is not active in the lung, but it is rapidly metabolized to des-ciclesonide (RM1) the active metabolite. It is proposed to have high lung deposition because of the high fine particle fraction of its solution formulation, and low systemic toxicity because of the low absorption of the parent compound in the gastrointestinal tract.

The applicant proposes the use of ciclesonide for the maintenance treatment of asthma in adult and \_\_\_\_\_ patients— years of age and older. They are also proposing its use in subjects who are taking oral corticosteroids (OCS) as a means of decreasing the dose of OCS.

For patients \_\_\_\_\_ years of age the applicant proposes a dose of \_\_\_\_\_  
 — In this age group, the proposed dose is the same for subjects previously treated with bronchodilators only as for those previously treated with other inhaled corticosteroids (ICS). For adults and adolescents 12 years of age and older, doses of 80 mcg taken \_\_\_\_\_ a day to \_\_\_\_\_ a day, are recommended. For patients with mild to moderate asthma previously treated with ICS, or previously treated with bronchodilators alone, a starting dose of 80 to \_\_\_\_\_ mcg \_\_\_\_\_ a day is recommended. \_\_\_\_\_, and for patients already taking OCS a starting dose of 320 or \_\_\_\_\_ mcg twice a day is recommended. \_\_\_\_\_

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#### 1.2. State of Armamentarium for Indication

Currently there are five different inhaled corticosteroids available for the treatment of asthma. Fluticasone is available alone as Flovent® HFA-134a MDI or in combination with salmeterol in ADVAIR® dry powder inhaler (DPI). The HFA formulation of Flovent was approved on May 14, 2004, and is recommend for the prophylactic treatment of asthma in patients 12 years and older. (The previously available form of fluticasone, Flovent Rotadisk, is being taken off of the market.) Advair contains fluticasone in a dry powder formulation as Advair Diskus, and is approved for the prophylactic treatment of asthma in all subjects 12 years of age and older. It is also approved for the treatment of subjects 4 to 11 years of age who are symptomatic on ICS. The dosing regimen is twice daily for Flovent and Advair.

Beclomethasone (QVAR®) is approved for treatment of asthmatics 5 years and older and is administered twice daily. Triamcinolone (Azmacort®) and flunisolide (Aerobid®) are both approved for patients 6 years and older, and both are also administered twice daily. Budesonide (Pulmicort Turbuhaler®) is approved for treatment of patient 6 years and older. The recommended starting doses are given twice daily. However, patients who are stable on

ICS can be switched to Pulmicort Turbuhaler using a once daily regimen. Budesonide (Pulmicort Respules®) is the only inhaled corticosteroid preparation available for very young children (approved for subjects 12 months to 8 years). However the respules must be used with a jet nebulizer.

If approved, ciclesonide would be the first inhaled corticosteroid available to a wide range of patients in a — daily regimen. In addition, it is purported by the applicant to have less systemic toxicity due to the high lung deposition and to the fact that it is inhaled in an inactive form which has low absorption in the gastrointestinal tract.

b(4)

### 1.3. Important Milestones in Product Development

IND 53,391 was submitted in 1997 and then inactivated because the Agency felt the preclinical and clinical data were inadequate to support the proposed dose. After making changes to the protocols and obtaining phase I clinical data in Europe, the IND was reactivated in January 1998 by Byk Gulden (US Representative – Altana).

An end-of-phase 2 meeting was held on October, 1999. At that time the Agency recommended that once daily vs twice daily dosing should be compared. The Agency also noted that the claim of a \_\_\_\_\_ would require replicated studies comparing HPA-axis suppression in subjects treated with doses of ciclesonide and fluticasone that had identical efficacy.

Ownership of the IND was transferred to Aventis Pharmaceuticals in May 2001. In March of 2002 Aventis requested combining studies 323 and 324 into one because of difficulty in recruitment. Since the protocols were identical the Agency stated that it would be acceptable to combine the results for statistical analysis. However, the Agency also noted that this procedure might pose a significant risk if the once daily regimens were not successful. In that event, there would not be adequate trials to demonstrate efficacy of the twice daily regimens.

On June 2, 2003 a meeting was held with the Applicant to discuss the findings of an excess of cataracts in subjects with moderate to severe asthma who had been treated with ciclesonide in study 323/324. The Agency noted that the findings were of concern even though the studies had not been designed to detect cataracts. The applicant was instructed that in order to resolve this issue, a study of a minimum of 1, and preferably 3 years duration, including appropriate examinations and controls, would have to be conducted. The applicant subsequently agreed to conduct a 1-year study to specifically look at the incidence of cataracts in ciclesonide-treated subjects. Patient enrollment was completed in early 2004, but the results will not be available for review prior to the PDUFA date for this NDA.

The applicant was informed at the June 2003 meeting that if ophthalmologic safety could not be demonstrated prior to the submission of the NDA, and the drug was otherwise approvable, then it might be necessary to include a summary of the finding of excess cataracts in ciclesonide-treated subjects in trial 323/324 in the Alvesco® label.

On August 7, 2003 a meeting was held with the applicant to discuss the results of a review of previously submitted toxicology studies. In 1997 Byk Gulden, the original owner of ciclesonide, submitted the results of studies in dogs showing “spermiogenic disturbance”. To refute these results, Aventis constituted an outside Pathology Working Group to review

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the results. According to the Working Group, the original report was incorrect and all of the previously reported abnormalities were, in fact, artifacts. After extensive discussion within the Agency, it was concluded that the finding represented a low level of concern regarding possible risk to human subjects. However, the issue would have to be readdressed at the time of the NDA review

APPEARS THIS WAY ON ORIGINAL