Clinical Pharmacology Review

NDA:	22-124
Submission Date:	May 24, 2007
Name:	Omnaris™ (ciclesonide) nasal spray
Sponsor:	Altana / Nycomed
Type of Submission:	Complete Response to NDA Approvable Letter
Reviewer:	Partha Roy, Ph.D.
Date:	November 7, 2007

Background:
Ciclesonide Aqueous Nasal spray received approval for the treatment of the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients ≥ 12 years of age on October 7, 2006. At the same time, NDA 22-124 for patients under 12 years of age was given an approvable action. The deficiencies cited in the action letter for NDA 22-124 were inadequate efficacy and safety in this age group.

Submission:
The purpose of this submission is to provide efficacy and safety data in response to the deficiencies outlined within the approvable action associated with the use of OMNARIS™ (ciclesonide) Nasal Spray in children 2 to 11 years of age.

From the clinical pharmacology perspective, there is one new clinical study (M1-416) where HPA axis function was evaluated in children 2 to 5 years of age suffering from PAR. For the 6 to 11 year age group, no new HPA axis data are submitted.

Review:
HPA axis evaluation in patients 2 to 5 years of age

Study M1-405 was submitted as part of the original NDA 22-004 submission in which HPA axis evaluation was performed in PAR patients 2 to 5 years of age. Detailed review can be found in Dr. Sayed Al Habet's Clinical Pharmacology Review dated August 28, 2006. The study results have been incorporated in the approved Omnaris® label. Briefly, the differences (95% CI) from placebo in the mean change of 24-hr UFC from baseline after 6 weeks of treatment were -2.04 (-4.4, 0.3), -1.96 (-4.5, 0.6), and -1.76 (-4.3, 0.8) mcg/day for 200 mcg, 100 mcg, and 25 mcg dose groups, respectively. The corresponding differences (95% CI) from placebo in the mean change of AM plasma cortisol values were -1.04 (-2.7, 0.7), -0.36 (-2.1, 1.4), and -0.12 (-1.8, 1.6) mcg/dL, respectively (Table 1). Therefore, it was evident that the ciclesonide-treated groups had a numerically greater decline from baseline in both 24-hr UFC and AM plasma cortisol values compared to the placebo treated group.

Table 1. Summary of 24-hr UFC (mcg/day) and AM Serum Plasma Cortisol (mcg/dL) data after administration of different doses of Ciclesonide in children 2 to 5 years of age

	Treatment			
	Ciclesonide 200 mcg	Ciclesonide 100 mcg	Ciclesonide 25 mcg	Placebo
24 hr UFC (Uncorrected for Creatinine)				
Baseline N Mean (SD)	 22 11.8 (10.2)	 15 8.8 (4.4)	 16 12.6 (8.6)	 2 8.6 (3.7)
6 weeks N Mean (SD) LS Mean change from baseline	 22 6.9 (3.84) -3.55	 15 6.9 (3.74) -3.47	 16 7.4 (4.03) -3.27	 18 9.0 (2.69) -1.51
Treatment difference (95% CI)	-2.04 (-4.4, 0.3)	-1.96 (-4.5, 0.6)	-1.76 (-4.3, 0.8)	
AM Plasma Cortisol				
Baseline N Mean (SD)	 28 9.7 (3.7)	 27 9.6 (4.2)	 28 10.3 (3.3)	 30 8.6 (3.7)
6 weeks N Mean (SD) LS Mean change from baseline	 28 8.8 (2.8) -1.07	 27 9.4 (4.5) -0.39	 28 10.0 (3.7) -0.15	 30 10.2 (3.6) -0.03
Treatment difference (95% CI)	-1.04 (-2.7, 0.7)	-0.36 (-2.1, 1.4)	-0.12 (-1.8, 1.6)	

Reference: Refer to Clinical Pharmacology Review of NDA 22-004 (August 28, 2006)

The present submission includes a new study (M1-416) where HPA axis function was evaluated in PAR patients of 2 to 5 years of age using only AM plasma cortisol measurement. The 24 hr-UFC was not measured in this study.

Study M1-416

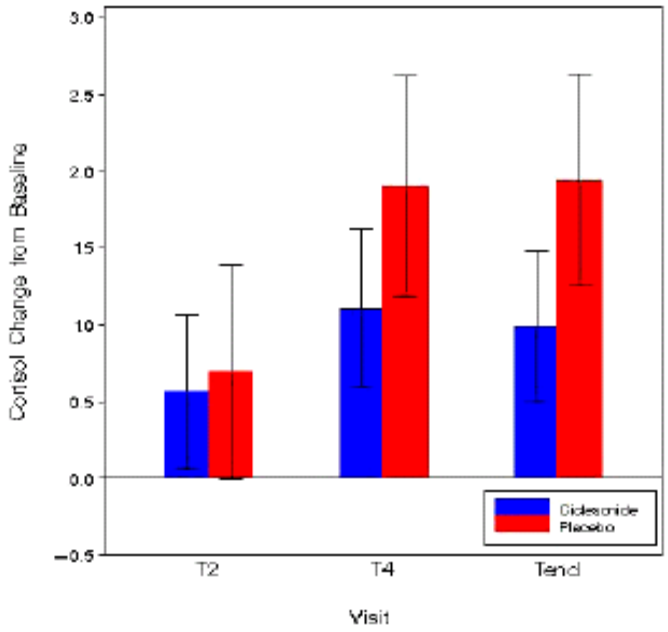
Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Clinical Trial Designed to Assess the Safety and Tolerability of Ciclesonide (200 mcg Once Daily), Applied as a Nasal Spray for Twelve Weeks, in the Treatment of Perennial Allergic Rhinitis (PAR) in Pediatric Patients 2-5 Years of Age

Objectives: To evaluate the safety, tolerability and efficacy of ciclesonide 200 mcg. Morning (prior to 9AM) serum samples were collected to evaluate serum cortisol at screening (-14 to -7 days before the 1st dose), 6-weeks and 12-weeks following once daily administration of intranasal spray.

Design: Each patient received Ciclesonide (200 mcg q.d.) nasal spray (2 actuations / nostril / day) for 12 consecutive weeks. Changes from baseline in serum cortisol levels and the 95% C.I. for the treatment difference (treatment – placebo) were calculated based on an ANCOVA model with factors of age, sex, treatment, center, & baseline cortisol.

Results: Both ciclesonide and placebo groups showed mean increases in serum cortisol levels from baseline after both 6 and 12 weeks of once-daily treatment. The observed mean increase in the ciclesonide group was relatively lower than in the placebo group (Figure 1).

Figure 1. Changes of AM serum cortisol from baseline at 6 weeks (T2), 12 weeks (T4) and at patient's last on-treatment visit (Tend).



The mean difference (95% CI) from placebo in the mean change in plasma cortisol from baseline to endpoint (patient's last on-treatment visit) i.e. approximately 12 weeks was -0.95 (-2.63, 0.72). The sponsor concluded that for AM serum cortisol, no clinically significant difference between treatment groups was indicated by the inclusion of zero in the 95% confidence interval for the treatment difference from placebo. These data are generally consistent with the results from the previous HPA-axis studies with ciclesonide.

Table 2. AM Serum cortisol (mcg/dL) at baseline, 6 weeks and endpoint (patient's last on-treatment visit) and changes from baseline and treatment difference

	Treatment	
	Ciclesonide 200 mcg	Placebo
Baseline N Mean (SD)	 78 9.86 (3.94)	 40 9.85 (3.80)
6 weeks N Mean (SD) LS Mean change from baseline	 78 10.27 (4.42) 0.56 (0.50)	 40 10.53 (5.16) 0.69 (0.70)
Treatment difference (95% CI): -0.13 (-1.94, 1.57); p = 0.876		
Baseline N Mean (SD)	 79 9.83 (3.93)	 40 9.85 (3.80)
Endpoint N Mean (SD) LS Mean change from baseline	 79 10.80 (4.21) 0.99 (0.49)	 40 11.74 (4.86) 1.94 (0.69)
Treatment difference (95% CI): -0.95 (-2.63, 0.72); p = 0.262		

Based on ANCOVA model with factors for age, sex, baseline cortisol, and treatment

Reviewer's comments:

1. The number of subjects who received 200 mcg ciclesonide in the new M1-416 study is significantly greater compared to the previous M1-405 study (79 vs. 28).

2. The study M1-405 evaluated HPA-axis function across 3 dose strengths of 25, 100 and 200 mcg while study M1-416 evaluated the highest dose strength of 200 mcg.

3. The study M1-416 is a 12-week evaluation compared to 6-week evaluation in study M1-405.

4. The 24-hr UFC is the accepted standard for the evaluation of the effect of corticosteroid on HPA-axis function in pediatric patient population. This measure is generally considered more sensitive and reliable than AM plasma cortisol. In study M1-416, 24-hr UFC was not measured.

5. In study M1-416, the mean treatment differences (95% CI) at 6 weeks and 12 weeks were -0.13 (-1.94, 1.57) and -0.95 (-2.63, 0.72), respectively.

6. In study M1-416, increases from baseline in mean AM serum cortisol after both treatment and placebo after 6 and 12 weeks were noted. Therefore, the treatment group showed a relative decrease compared to placebo. This apparent increase in cortisol level following treatment likely indicates the variability and unreliability of AM serum cortisol measurement.

7. In study M1-405, dose-dependent numerical decrease in both 24-hr UFC and AM serum cortisol in children 2 to 5 years of age were observed.

8. Upon cross-study comparison, it has been noted that once daily administration of 200 mcg ciclesonide at 12 weeks (from study M1-416) produces a comparable AM cortisol level decrease to 6 weeks administration (from study M1-405) suggesting no change beyond 6 weeks. However, within the study M1-416, cortisol level decrease at 12-week was numerically greater than at 6-week while the 6-week data across the two studies are not numerically comparable.

Conclusion and Recommendation

HPA-axis data, as discussed above from studies M1-416 and M1-405, strongly corroborate the view that the AM serum cortisol measurement is highly variable, often unreliable and not discriminatory and hence is only considered supportive data for this evaluation. Also, the previously submitted study M1-405 exhibited consistent trend towards dose-dependent numerical decrease in cortisol following administration of ciclesonide for both 24-hr UFC and AM plasma cortisol measurements. Since both 24-hr UFC and AM serum cortisol data from study M1-405 had already been summarized in the currently approved label for Omnaris® and the AM cortisol data obtained from study M1-416 is consistent with the overall trend observed in study M1-405, inclusion of this data in the label would not provide any additional useful information.

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/s/

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