CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-124s000

SUMMARY REVIEW

CROSS-DISCIPLINE TEAM LEADER & DIVISION DECISIONAL REVIEW

Date	November 21st , 2007
From	Lydia I Gilbert-McClain, MD, FCCP, Medical Team Leader
Through	Badrul A. Chowdhury, MD, PhD, Division Director
Subject	Cross –Discipline Team Leader Review
TO: NDA	22-124
Proprietary / Established (USAN) names	OMNARIS™/Ciclesonide
Dosage forms / strength	Nasal spray/ 50 mcg per actuation
Proposed Indication(s)	1. Treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children (b) (4) years of age and older.
Recommended	Complete Response

1. Introduction to Review

A new drug application for ciclesonide nasal spray was submitted to the Agency on December 21 2005 under 505 (b) (1) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50 to obtain marketing approval for ciclesonide nasal spray for the treatment of nasal symptoms with seasonal and perennial allergic rhinitis in adults and children (b) (4) years of age and older. Upon review of the application it was determined that efficacy and safety for adults and adolescent patients 12 years of age and older was established, however efficacy and safety for pediatric patients under 12 years of age was not. The NDA was (b) (4) for approval of ciclesonide nasal spray 200 mcg once daily for patients 12 years of age and older under NDA 22-004 on October 20, 2006. The indication for pediatric patients (b) (4) to 11 years of age was addressed under NDA 22-124 and this NDA was given an approvable action. This memo will address the Applicant's complete response to the Approvable letter to NDA 22-124. This memo will consider in greater detail the Division's evaluation of the efficacy support for the indication in patients (b) (4) to 11 years of age, extrapolation issues, safety, and adequacy of dosing (b) (4) .

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The sponsor for the original application was ALTANA, however the sponsor for the application is now NYCOMED. Although the original application was approved for patients 12 years of age and older, ciclesonide nasal spray has not yet been marketed in the U.S.
The deficiency stated in the action letter of October 20, 2006, was that the applicant had not established efficacy and safety of the product in children less than 12 years of age. In the action letter it was noted that the clinical studies conducted failed to show convincing evidence (b) (4) . To address the deficiency, the Applicant was asked to do the following:

- Conduct a clinical program to show substantial evidence of efficacy in at least the older children within the (b) (4) through 11 year age group and submit an adequate safety database that includes assessment of the effect of ciclesonide on the HPA axis, nasal safety, and

overall safety. The data need to be robust for the [redacted] (b) (4) 11 year age group.

The applicant submitted a complete response to the approvable letter on May 24, 2007. Upon review, the response was determined to be complete and the PDUFA goal date for this submission is November 24, 2007. The applicant submitted one efficacy study in patients 6 to 11 years of age with seasonal allergic rhinitis (Study # M1-417), one 12-week safety study in patients 2 to 5 years of age with perennial allergic rhinitis (Study # M1-416), and the previously reviewed studies (# M1-403 in patients 6 to 11 years of age with perennial allergic rhinitis, and # M1-405 a safety study in patients 2 to 5 years of age with perennial allergic rhinitis) to address the deficiency in the action letter.

3. CMC/Microbiology/Device

There are no unresolved CMC/device issues. The product under review is the same approved product under NDA 22-004.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved preclinical issues. The Applicant submitted one kinetic study in pregnant rats following oral administration. In this study, 20 female Wistar rats were given ciclesonide via gavage at a dose of 0.9 mg/kg/day during days 6 -21 post coitum and serum concentrations of ciclesonide and the des-ciclesonide (M1 metabolite) were measured at various time points. Systemic exposure in pregnant rats was confirmed based on serum concentrations of the active metabolite M1. Levels of M1 in the serum of the fetuses however were less than 0.13% compared to that of the dams suggesting a low penetration of ciclesonide and/or metabolite in the placenta. For further details see Dr. Huiqing Hao's Pharmacology/Toxicology review.

5. Clinical Pharmacology/Biopharmaceutics

Additional pharmacokinetic information was not submitted in this complete response. The Applicant measured AM serum cortisol levels in patients 2 to 5 years of age as an assessment of HPA axis function in study M1-416. The AM cortisol results from study M1-416 actually showed an increase in AM cortisol levels relative to placebo in the patients treated with ciclesonide but these results are unreliable. Serum AM cortisol measurement is not an adequate way to assess HPA axis effects because of the variability in a single measurement. Because of the diurnal pattern of cortisol secretion, a 24-hour assessment (serum or urine) of cortisol secretion is a more accurate way to assess cortisol effects. In a prior study (M1-405), cortisol results using 24-hour urine cortisol measurement showed a dose-related trend of decreased urine cortisol following treatment with ciclesonide nasal spray. The label already has data from 24-hour urine cortisol in the pharmacodynamic section of the label and the results from study M1-416 should not be added to the pharmacodynamic section of the label.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical

The pediatric development program comprises 2 efficacy studies in patients 6 to 11 years of age - M1-403 and M1-417, and two safety studies in patients 2 to 5 years of age – M1-405 and M1-416. Studies M1-403 and M1-405 were submitted and reviewed in the original NDA.

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The development program for ciclesonide nasal spray included two efficacy dose-ranging studies one in adults and adolescents 12 years of age and older with seasonal allergic rhinitis [SAR] (study CL-002), and one in pediatric patients 6 to 11 years of age with perennial allergic rhinitis [PAR] (study M1-403) using doses of 25 mcg, 100 mcg, and 200 mcg of ciclesonide nasal spray once daily. These studies were submitted and reviewed with the original NDA 22-004 submission. In study CL-002, only the 200 mcg dose showed statistical superiority over placebo. However, in the pediatric dose-ranging study, none of the doses of ciclesonide showed statistically significant improvement over placebo. The 200 mcg dose is currently approved in patients 12 years of age and older. The results of these 2 dose-ranging/efficacy studies are described in the product label. In this complete response, the Applicant submitted results of one study conducted in SAR patients 6 to 11 years of age with doses of 100 mcg and 200 mcg once daily (study M1-417). In this study (described in more detail below), only the 200 mcg dose showed statistical superiority over placebo whereas, the 100 mcg dose did not. This is an unusual observation for a nasally inhaled corticosteroid. Historically, with other corticosteroids, several doses are usually effective, and usually, half the adult dose has been studied and ultimately approved in children under 12 years of age. With systemically acting drugs, exposure data (AUC) is useful in guiding dose selection in the pediatric population, whereas, for locally acting drugs, PK has limited (if any) utility in informing dose selection. In this regard, there is the underlying recognition, that the dose selected for the pediatric population for locally acting drugs may in fact be higher than necessary for efficacy but with adequate assurance of safety, the use of the dose can be supported.

In the case of ciclesonide nasal spray, the dose that was shown to be effective in children 6 to 11 years of age for SAR is the same as the adult dose – 200 mcg once daily. (b) (4)

[redacted]

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The applicant conducted one efficacy study in patients 6 to 11 years of age (study M1-417) with SAR and one efficacy/dose-ranging study in patients with PAR (study M1-403). As stated earlier, study M1-403 was reviewed in the original application and did not show efficacy.

Study M1-417

This study was conducted in patients 6 to 11 years of age with a history of SAR for at least 2 years. These patients had a positive skin test (wheal 3 mm > control) to a seasonal allergen within 12 months of enrollment and had SAR of a severity that warranted treatment. Patients with grass and/or tree pollen allergens as well as patients with SAR due to fall allergens (excluding molds) participated. Patients with upper respiratory infections, nasal abnormalities such as polyps, or malformations, were excluded.

This was a 2-week double blind placebo-controlled study with a placebo run- in period of up to 21 days (for patients previously on an inhaled corticosteroid). For patients who were not previously on inhaled corticosteroids, the screening/placebo run-in period was 7 – 14 days. During the screening/placebo run-in period, the patients' caregivers recorded the patients' symptoms in an electronic diary twice daily. The standard symptoms of runny nose, itchy nose, sneezing, and nasal congestion, scored on a 0 (none) to 3 (severe)-point scale were recorded, and these 4 symptoms comprised the total nasal symptom score (TNSS). In order to be randomized, patients had to have a minimum TNSS (either AM or PM) of at least 6 for at least 5 of the last 7 days of the run-in period, and the score for rhinorrhea or nasal congestion needed to be of moderate severity (minimum score = 2). The primary efficacy endpoint was the change from baseline in the mean of the AM and PM r-TNSS. The baseline was taken as the average of the mean AM and PM scores obtained during the last 7 days of the screening period.

This study differs from the other allergic rhinitis studies in that an electronic diary was used to report the patients' symptoms. There were no paper diaries used in this study and no back-up hard copies of the electronic data were made by the applicant. The electronic diary used was the [redacted] (b) (4) Interactive Voice Recording System (IVRS). During the baseline and the treatment period, AM and PM patient diary data were provided by the parent/caregiver, using the IVRS. The parent/caregiver evaluated the patient's nasal symptoms over the 12 hours prior to the recording of the score (reflective) and over the last 10 minutes (instantaneous scores). Instructions for use of the IVRS were reviewed with the parent/caregiver at the baseline and randomization visit. The parent/ caregiver had to call in the patient's symptoms scores twice each day between 5:00 AM – 12 noon and between 5:00 PM – 12 midnight. Duplicate entries were not accepted by the system. There were minor discrepancies in the written instructions given to the parent/caregiver compared to the IVRS system in the definition of the symptom severity 1 as "very mild" (IVRS) or "mild" (investigator instructions to parent/caregiver). This discrepancy did not appear to affect the results. The entire operation of the IVRS (obtaining the data, and submitting it to the Applicant) was the responsibility of [redacted] (b) (4) the developer of the IVRS. A DSI audit of [redacted] (b) (4), as well as 3 of the study sites was requested.

Results

There were 349 males and 269 females randomized in this study. Of these, 215 patients were randomized to ciclesonide once daily, 199 to ciclesonide 100 mcg once daily, and 204 to placebo. A total of 588 patients completed the study. There was a statistically significant improvement (decrease in symptoms) with the ciclesonide 200 mcg once daily treatment compared to placebo for the primary endpoint (change from baseline in the mean of the AM and PM r-TNSS), whereas, the 100 mcg once daily dose of ciclesonide nasal spray was not statistically superior to placebo. Of note, the study was powered to detect a difference of 0.75 in the change from baseline in overall TNSS with a two-sided alpha level of 0.05, however, the effect size demonstrated was much less (0.39). The AM instantaneous score assessed as a secondary efficacy variable had a similar effect size (0.39). Another secondary efficacy variable was the physician-assessed nasal symptom score (PANS at endpoint (last treatment assessment) which showed statistically significant improvement over placebo for the ciclesonide 200 mcg once daily treatment arm. The effect size for the PANS was larger (0.92) than that of the caregiver TNSS; however, unlike the TNSS, the PANS was a comparison between baseline and Endpoint, and not the average over the 2-week treatment period. This difference in assessment of the symptom score may account for the widely disparate results. The efficacy data are shown in the table below.

Table 1. Mean changes in reflective total nasal symptom score and instantaneous total nasal Symptom score in 1 seasonal allergic rhinitis trial in children 6 to 11 years of age

Treatment	n	Baseline*	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
Reflective total nasal symptom score						
Ciclesonide 200 mcg	215	8.25	-2.46	-0.39	(-0.76, -0.02)	0.040
Ciclesonide 100 mcg	199	8.41	-2.38	-0.32	(-0.69, 0.06)	0.103
Placebo	204	8.41	-2.07			
Instantaneous nasal symptom score						
Ciclesonide 200 mcg	215	7.72	-2.21	-0.44	(-0.81, -0.06)	0.022
Ciclesonide 100 mcg	199	7.67	-2.09	-0.31	(-0.69, 0.07)	0.107
Placebo	204	7.84	-1.78			

*Mean of AM and PM score from reflective total nasal symptom score; Mean of AM score for Instantaneous total nasal symptom score; Maximum = 12

The effect size seen in the individual symptoms both for the reflective and the instantaneous scores was very small. The individual findings for the reflective symptom score is shown in the table below.

Table 2. Mean changes in Reflective symptom scores for Individual Nasal Symptoms

	Ciclesonide 200 mcg (n = 215)	Placebo (n = 204)	Ciclesonide vs. placebo (95% CI)
Nasal Congestion			0.13 (0.03, 0.23)
Baseline (mean)	2.42 (0.50)	2.41 (0.48)	
Change from baseline	0.64 (0.04)	0.51 (0.04)	
Nasal Itching			0.09 (-0.02, 0.19)
Baseline (mean)	2.02 (0.63)	2.10 (0.60)	
Change from baseline	-0.65 (0.04)	-0.56 (0.04)	

Sneezing Baseline (mean) Change from baseline	 1.72 (0.71) -0.57 (0.04)	 1.74 (0.68) -0.55 (0.04)	0.08 (-0.02, 0.18)
Runny nose Baseline (mean) Change from baseline	 2.09 (0.66) -0.61 (0.04)	 2.16 (0.60) -0.57 (0.04)	0.10 (-0.01, 0.22)

7.1.3. Other efficacy studies

There were no other primary efficacy studies in patients under 12 years of age. Although efficacy was assessed in study M1-416, this was a study designed to assess the safety of ciclesonide 200 mcg once daily for 12 weeks in patients 2 to 5 years of age with PAR. The physician assessment of nasal symptoms, and 24-hour reflective TNSS were used to evaluate efficacy as a secondary objective. In this study, the reflective TNSS supported efficacy of the ciclesonide 200 mcg once daily dose (diff vs. placebo -0.9 [-1.6, -0.1]; p =0.021)

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

The comments in the primary medical officer's reviews are consistent with the conclusions in this CDTL memo and there are no disagreements that need to be addressed. In the secondary statistical review, an analysis of responder profile is described to illustrate the effect size of ciclesonide in SAR patients. The secondary reviewer notes a maximum treatment difference of 8.7% and makes the interpretation that at most when 100 patients are treated only 8 could benefit from the drug. On its face this effect seems quite small, however for regulatory decision making purposes we do not address demonstration of efficacy using that approach. Efficacy over the treatment period was demonstrated as indicated by superiority over placebo. Furthermore, the Division has not defined a minimal clinically important difference for the allergic rhinitis population. Given the variability in disease progression, and the varied and sometimes fairly large placebo effect that has been seen in allergic rhinitis clinical trials, it is unlikely that a minimum effect size could be defined with any degree of certainty.

7.1.5. Pediatric use/PREA waivers/deferrals

The Applicant has addressed all the age groups for which this drug product should be studied. The applicant has conducted studies in patients with allergic rhinitis down to 2 years of age. Pediatric Research Equity Act (PREA) requirements were addressed in the action letter for ciclesonide nasal spray under NDA 22-004. The Applicant was granted a wavier for studies in patients from ages birth to less than 2 years of age. Waiving studies in patients less than 2 years of age for this product is consistent with the Division's practice of not requiring studies with nasally inhaled corticosteroids in patients less than 2 years of age primarily because of safety concerns and local toxicity. The applicant has one other pediatric assessment under PREA to be addressed – namely, an assessment of the effects of ciclesonide nasal spray on growth velocity in children. The Division being aware that the Applicant had conducted a growth study in children using orally inhaled ciclesonide (ciclesonide MDI), stated in the action letter (NDA 22-004) that provided the systemic exposure from another formulation is higher than the systemic exposure from the nasal spray, then a linear growth study conducted with a formulation of ciclesonide other than the nasal formulation may be adequate to address this pediatric assessment. The growth study conducted using ciclesonide HFA mini dose inhaler (Alvesco) is currently under review in a complete response to NDA 21-658. The

applicant indicated in correspondence dated Oct 18, 2007 to NDA 22-004 (ciclesonide nasal spray) that they intend to submit a labeling supplement containing new pharmacokinetic data relating to the comparison of the systemic exposure of ciclesonide nasal spray versus orally inhaled ciclesonide MDI. The submission will also include summary information from the growth study conducted with ciclesonide MDI (study 343) that is currently under review under NDA 21-658 (Alvesco). The planned submission date is December 20, 2007. The Applicant intends this submission to fulfill the required pediatric postmarketing study commitment associated with the assessment of the effects of ciclesonide nasal spray on growth velocity in children identified within the October 20, 2006, approval letter (NDA 22-004) for Omnaris™ Nasal Spray.

7.1.6. Discussion of notable efficacy issues

Scientifically, the pathophysiology and the disease course of allergic rhinitis are considered to be sufficiently similar in adults and children. Therefore, if the effects of the drug are sufficiently similar in adults and pediatric patients a conclusion of efficacy can be extrapolated from the adult efficacy. The Division has used the paradigm of extrapolation in prior applications for allergic rhinitis to support efficacy in the pediatric population. The best examples have been with the systemically acting drugs with dose selection supported by pharmacokinetic data that provide information on bioavailability and systemic exposure. The most recent example using extrapolation has been with levocetirizine (NDA 22-064) approved May 26, 2007 for relief of symptoms in allergic rhinitis (seasonal and perennial) and the treatment of skin manifestations of chronic idiopathic urticaria in patients 6 years of age and older. There were no efficacy studies conducted in allergic rhinitis patients under 12 years of age with a dose of 2.5 mg once daily, yet based on the demonstrated efficacy of the 2.5 mg and 5 mg dose in adults, and the pharmacokinetic findings of systemic exposure of levocetirizine 5 mg in children 6 to 12 years of age, the dose of 2.5 mg was approved for use in pediatric patients 6 to 11 years of age. Extrapolation has regulatory support and the paradigm is outlined in the 2007 Pediatric Research Equity Act (PREA) renewal (HR 3580 pg 45) in the following statements:

(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.

(i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

(iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

Extrapolation of efficacy of a locally acting drug becomes more of a challenge because there needs to be the assurance that the effects of the drug are the same in adults and children. In the case of ciclesonide, it is unclear whether the drug effects are the same in adults and children and the overall body of evidence suggests that the effects may be different. Ciclesonide is a pro-drug which is metabolized by in situ esterases to a pharmacologically active metabolite des-ciclesonide. In the allergic rhinitis adult studies, the effect size seen for the patients 12 – 17 years of age was by far much smaller than the effect size seen in the 18 – 64 year old age

group. In subgroup analysis, statistically significant results are not expected in all subgroups due to the reduced sample size and the natural variation expected when conducting multiple analyses, but the magnitude of effect size was only 0.26 and 0.12 for SAR and PAR respectively compared to 0.89 and 0.60 for the 18 – 64 age group (*Primary Statistical review NDA 22-004- Ms Feng Zhou*). The Division has not made a determination of a minimum effect size for allergic rhinitis trials as such a determination would be difficult if not impossible to do given the variability that can be seen in this patient population. Therefore, in spite of the smaller effect size, given that the totality of the evidence supported efficacy in the entire population, the drug was approved in patients 12 years of age and older. Although the 200 mcg dose demonstrated efficacy for PAR in the adults, this was not demonstrated in patients 6 to 11 years of age. The reason for this is unclear. It is generally recognized that symptoms due to PAR are more difficult to treat than symptoms of SAR and one reason for the disparate PAR results in adults and children may be that the drug effects are different in the two populations. Keeping in mind that ciclesonide is a pro-drug and pharmacological activity is dependent upon the conversion via enzymatic cleavage to the active metabolite; a difference in enzymatic profile in the two populations may lead to differences in response. With questions about the drug effects in the pediatric population, extrapolation of efficacy becomes less reliable for this drug product. Secondly, efficacy has not been demonstrated with doses less than 200 mcg once daily. Using the same adult dose of 200 mcg in the 2 year old age group raises significant safety concerns given the evidence of systemic exposure (detection of des-ciclesonide in blood and dose-related trends in urine cortisol levels) in patients 2 to 5 years of age. An extensive safety evaluation would be necessary before the 200 mcg dose could be considered for use in patients less than 6 years of age.

7.2. Safety

The safety database includes 1541 patients 2 to 11 years of age. Of these, 1096 [913 patients aged 6 to 11, and 183 patients aged 2 to 5 years] were exposed to ciclesonide in doses ranging from 25 mcg to 200 mcg once daily. Of this number, a total of 496 patients were treated with ciclesonide 200 mcg once daily, 398 were exposed to ciclesonide 100 mcg once daily, and 202 were exposed to ciclesonide 25 mcg once daily. This safety database includes patients from the 2 studies submitted in the complete response, as well as the 2 studies submitted in the original NDA application.

7.2.1. General safety considerations

The overall mean exposure to ciclesonide 200 mcg once daily was 49 days in patients 2 to 11 years of age. Children 2 to 5 years of age (6 weeks and 12 weeks study duration) had a mean exposure of 70 days compared to the older children who had a mean exposure of 43 days (study duration 2 weeks and 12 weeks).

7.2.2. Safety findings from submitted clinical trials

There were 2 deaths in the studies none of which were related to the study drug or any protocol procedure. Two female patients age 6 and 7 (cousins) died in an automobile accident. Most adverse events were mild to moderate in intensity. More patients in the placebo group (3.8%) withdrew from the studies because of an adverse event compared to the ciclesonide treatment groups and the incidence of withdrawals due to AEs was lowest in the ciclesonide 200 mcg group (1.6%). The AEs leading to withdrawal were varied with no clear pattern. The events included hypersensitivity, sinusitis, upper respiratory tract infection, urinary tract infection, varicella, asthma, nasal discomfort, and pharyngolaryngeal irritation/pain. The most common

(incidence of ≥ 3%) adverse events were headache, nasopharyngitis, and pharyngolaryngeal pain. Of these events, only the latter 2 were reported more frequently in the placebo group. There were no reports of nasal ulcerations or perforations.

7.2.3. Safety update

The safety update in this submission include the safety data from studies M1-416 and M1-417 in the pediatric population and one adult study (TBN-15/008) conducted in Japan. There are two ongoing studies in adults using ciclesonide HFA nasal aerosol. The data from these studies are blinded and do not contribute meaningful information to the database. The Japanese study used doses of 400 mcg twice daily, 400 mcg once daily, and 200 mcg twice daily. In that study, nasopharyngitis was the most common AE and was seen in all treatment groups (including placebo) with no clearly defined dose relationship. There were no deaths or serious AEs in this study.

7.2.4. Immunogenicity

Not applicable

7.2.5. Special safety concerns

Like all corticosteroids, ciclesonide has certain class effects such as local toxicity effects, risks of infection, potential for growth suppression, and HPA axis suppression and the package insert carries class labeling for corticosteroid-related effects.

7.2.6. Discussion of primary reviewer's comments and conclusions

The primary medical officer's comments and conclusions are consistent with those of the CDTL. There was a difference of opinion between the primary and secondary statistical reviewers in the interpretation of the Applicant's multiplicity procedure for their statistical analysis plan. I concur with the interpretation of the statistical secondary reviewer who concludes that for study 417 if the high dose demonstrates efficacy then the efficacy of the low dose will be considered but at the same time, the secondary endpoints can also be considered. (See *Secondary review Page 7 Qian Li – statistical reviewer for more details)*

7.2.7 Discussion of notable safety issues

There are no outstanding safety issues to be addressed.

8. **Advisory Committee Meeting**

An advisory committee (AC) meeting was not held for this complete response. The product is approved in patients 12 years of age and older and there are no issues in the patient population under 12 years of age that warrant discussion at an AC meeting.

9. Other Relevant Regulatory Issues

None

10. Financial Disclosure

There are no financial disclosure issues.

11. Labeling

(b) (4)

(b) (4)

11.1. Proprietary name

There has been no change to the proprietary name OMNARIS.

11.2. Physician labeling

(b) (4)

11.3 Carton and immediate container labels

There are no carton or container issues as the applicant has not made any changes to the approved carton/containers.

11.4 Patient labeling/Medication guide

The Applicant updated the Patient Instructions for Use to include the indication of treatment of seasonal allergy symptoms in patients 6 years of age and older. This product does not carry a Medication Guide and none is warranted.

12. DSI Audits

Three investigator sites – 3872 (Dr Jeffrey Wald [n = 16]), 4777 (Dr. William Storms [n=18]), and 3482 (Dr. Ita Tripathy [n=13]) from study M1-417 were selected for audit based on the number of subjects enrolled at these sites and discrepancies noted in the amount of missing symptom diary data relevant to investigator comments. In addition the CRO developer of the (b) (4) was audited. There were no major problems noted at the three investigator sites and two sites # 3872 and # 3482 received a final DSI classification of NAI (no deviation from regulations – data acceptable). The preliminary report for study site #4777 indicated that there were no irregularities but the final classification is pending. The preliminary report for the inspection of (b) (4)

(b) (4)

The summary covered the salient inspectional findings and DSI's recommendations are based on several in-depth discussions with the field investigators and no additional issues are anticipated.

13. Conclusions and Recommendations

The Applicant has demonstrated efficacy of ciclesonide nasal spray 200 mcg for the treatment of the nasal symptoms of SAR in pediatric patients 6 to 11 years of age. (b) (4)

Under those circumstances, an extrapolation could then be made to extend the indication to SAR if there are already adult studies demonstrating efficacy in SAR. The second aspect of the efficacy issue for the pediatric population is that, in the development program with ciclesonide nasal spray only the 200 mcg dose was effective. (b) (4)

13.1. Recommended regulatory action

The regulatory action will be approval of ciclesonide nasal spray 200 mcg once daily for the treatment of the symptoms of seasonal allergic rhinitis in patients 6 years of age and older. (b) (4)

The indications for ciclesonide nasal spray will be separated out as follows in the label:

- Seasonal allergic rhinitis

Ciclesonide Nasal Spray 200 mcg once daily is recommended in adults and children 6 years of age and older.

- Perennial allergic rhinitis

Ciclesonide Nasal Spray 200 mcg once daily is recommended in adults and children 12 years of age and older.

13.2. Safety concerns to be followed postmarketing

There are no unique safety concerns to be followed postmarketing.

13.3. Risk Minimization Action Plan

There are no Risk Minimization Action Plans other than labeling.

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)
The applicant has an outstanding postmarketing commitment under PREA – assessment of growth effect. In correspondence dated October 18th, 2007 to NDA 22-004, the Applicant indicates that they intend to submit data to fulfill this commitment in December 2007. The applicant also has a postmarketing study commitment to conduct a safety study to evaluate the effects of ciclesonide nasal spray on the HPA axis. The study will be conducted using the labeled dose and at least one higher dose of ciclesonide nasal spray. The date for submission of the final study report is May 2008.

13.5. Comments to be conveyed to the applicant in the regulatory action letter
There are no deficiency comments to be conveyed in the action letter for NDA 22-124. (b) (4)

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/s/

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11/21/2007 12:57:41 PM
MEDICAL OFFICER

Badrul Chowdhury
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I concur