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*APPLICATION NUMBER:*  
**202129Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 23, 2011
<b>From</b>	Theresa M. Michele, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 202-129
<b>Supplement#</b>	
<b>Applicant</b>	Nycomed GmbH
<b>Date of Submission</b>	March 21, 2011
<b>PDUFA Goal Date</b>	January 21, 2012
<b>Proprietary Name / Established (USAN) names</b>	Ciclesonide nasal aerosol (HFA)
<b>Dosage forms / Strength</b>	Nasal inhalation/ 74 mcg once daily
<b>Indication</b>	treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older
<b>Recommended:</b>	Approval

### 1. Introduction

Sunovion Pharmaceuticals (Sunovion) submitted this original 505(b)(1) new drug application (NDA 202-129) for ciclesonide nasal aerosol (HFA formulation [CIC-HFA]), on March 21, 2011 as the US agent on behalf of Nycomed GmbH. CIC-HFA is a nasal corticosteroid proposed for the treatment of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents 12 years of age and older. The drug substance, ciclesonide, is approved in two other formulations, an aqueous nasal spray (Omnaris) for the treatment of SAR and PAR, and an HFA inhalational aerosol (Alvesco) for the treatment of asthma. Compared to the approved Omnaris Nasal Spray, this application provides for a new formulation (HFA aerosol) and seeks a broader indication of treatment of symptoms of SAR and PAR, which would include ocular symptoms as well.

The proposed indications for CIC-HFA are supported by efficacy and safety data from three pivotal trials, two in patients with SAR and one in patients with PAR, along with a dose ranging trial in patients with SAR. Additional safety data included a 6 week HPA axis trial, and an open label safety extension to the PAR trial out to 12 months.

The PDUFA due date for this application is January 21, 2012. This review will focus on the efficacy claims for seasonal and perennial allergic rhinitis, including ocular symptoms and quality of life, along with local safety issues. A primary concern for the application is the occurrence of two nasal septal perforations in the pivotal SAR trials.

## 2. Background

### 2.1. *Related drugs: issues with nasal corticosteroids*

CIC-HFA is a nasal corticosteroid. There are 8 other nasal corticosteroids currently approved for SAR and PAR: triamcinolone (Nasacort HFA Nasal Aerosol, Nasacort AQ Nasal Spray), beclomethasone (Beconase AQ), fluticasone propionate (Flonase), fluticasone furoate (Veramyst), mometasone (Nasonex), budesonide (Rhinocort Aqua), flunisolide (Nasarel), and ciclesonide (Omnaris). All are aqueous suspension formulations except for Nasacort HFA. Because Nasacort HFA was never marketed in the US, if approved, CIC-HFA would represent the first nasal HFA formulation on the US market.

All nasal corticosteroids carry standard warnings regarding local and systemic corticosteroid effects including development of glaucoma, posterior subcapsular cataracts, worsening of infections, hypercorticism, adrenal suppression, and reduction of growth velocity in children. In addition, nasal corticosteroids are known to cause local nasal adverse events, including epistaxis, nasal ulceration, *Candida albicans* infections, and impaired wound healing. Due to the local nasal effects, nasal steroids carry warnings to avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma.

Nasal corticosteroids also have a standard warning regarding nasal septal perforations. This is a rare event that has been observed in post-marketing surveillance but prior to this application, had not been reported in pre-marketing trials with nasal corticosteroids. Nasal septal perforations related to the povidone excipient were observed in pre-marketing trials of olopatadine hydrochloride (Patanase), a nasal antihistamine. In a 12 month safety trial of olopatadine, nasal septal perforations were reported in one patient treated with the povidone formulation of olopatadine and two patients in the placebo group (vehicle nasal spray containing povidone). No perforations were reported in a 12 month safety trial of the approved olopatadine formulation not containing povidone.

### 2.2. *Regulatory history*

Data from the two other approved formulations of ciclesonide are referenced in this NDA. These include:

- Alvesco (ciclesonide inhalational aerosol, HFA):
  - NDA 21-658: Approved January 10, 2008 for the maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older
- Omnaris (ciclesonide nasal spray)

- NDA 22-004: Approved October 20, 2006 for the treatment of nasal symptoms associated with SAR and PAR in patients 12 years of age and older
- NDA 22-124: Approved November 21, 2007 for the treatment of nasal symptoms associated with SAR in pediatric patients 6-11 years of age

(b) (4)

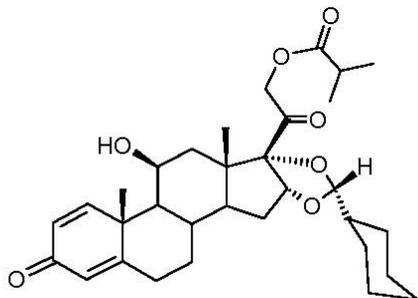
CIC-HFA was studied under IND 74,674. Sunovion holds this IND and has submitted appropriate right of reference to this as well as to related product INDs (IND 65,488, ciclesonide nasal spray and IND 53,391, ciclesonide inhalation aerosol). Standard development milestone meetings were held for the program, including a pre-IND meeting on October 16, 2006, an End of Phase 2 meeting on December 15, 2008, and a pre-NDA meeting on November 3, 2010. Key points from these meetings that are relevant to the NDA review include the following:

- [REDACTED] (b) (4)
- 74 and 148 mcg doses appropriate for dose ranging in adults
- Replicate SAR trials and one trial in PAR sufficient for approval if robust efficacy demonstrated
- ECG monitoring, ocular safety, and extensive chemistry/hematology evaluations from the Alvesco and Omnaris programs would not require repetition in the CIC-HFA program
- Growth study with Alvesco acceptable to fulfill requirement for a growth study for CIC-HFA
- 12 month data from the PAR extension study could be submitted in the 120 day NDA update
- Data from the scintigraphy study would not be included in the product label

### 3. CMC/Device

The drug substance of CIC-HFA is a non-halogenated glucocorticoid having the chemical name pregna -1,4-diene-3,20-dione, 16,17-[[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11 $\beta$ ,16 $\alpha$ )-. Ciclesonide is delivered as the R-epimer. The empirical formula is C<sub>32</sub>H<sub>44</sub>O<sub>7</sub> and its molecular weight is 540.7. Ciclesonide is a white to yellow-white powder. The CMC information for the drug substance was previously reviewed and found acceptable.

The structural formula is shown in Figure 1.

**Figure 1: Ciclesonide structural formula**

The drug product is a solution of ciclesonide in (b) (4) ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an (b) (4) canister to provide 30 or 60 actuations and sealed with a metering valve. A plastic actuator, which includes a dose counter, is included as part of the finished drug product. The drug formulation and the canister and valve combination are exactly the same as those used in the approved drug product, Alvesco (ciclesonide) Inhalation Aerosol. The assembled inhaler includes the canister containing the drug product and the actuator, which has a dose counter built in.

Dr. Arthur Shaw, the CMC reviewer, found that the ruggedness of the assembled inhaler is problematic. Drop tests show that a) the canister can be separated from the actuator and b) the dose counter can give incorrect counts after dropping. Therefore, the applicant is being asked to improve the ruggedness of the device. This will be a post-marketing commitment (PMC) rather than a post-marketing requirement (PMR) for the following reasons: 1) the device functions properly when the canister is reinserted into the actuator, 2) dose counters are not required for nasal products, and 3) under-counting of doses does not pose the same safety issue for an allergic rhinitis product than it would for an asthma product. In addition, information will be added to the patient instructions for use on 1) how to reassemble the inhaler if it comes apart after being dropped, and 2) warning the patient that the dose counter may be inaccurate if the inhaler is dropped.

The ex-actuator dose delivered from the to-be marketed inhaler is 37 mcg. The corresponding ex-valve dose is 50 mcg. The concentration of drug in the formulation is (b) (4). One spray in each nostril gives a total daily dose of 74 mcg. For the purposes of this review, all doses will be referred to as the ex-actuator dose.

## 4. Nonclinical Pharmacology/Toxicology

Non-clinical data supporting Alvesco were used to support this application because Alvesco and CIC-HFA have the same formulation. Complete toxicology programs were conducted with ciclesonide to support clinical administration by the inhalation and intranasal routes. Ciclesonide has a toxicological profile typical of glucocorticoids. Major toxicities observed in animal studies include immunosuppression, decreased body weights, slight increases in blood triglyceride and cholesterol levels, adrenal suppression, and lymphoid tissue atrophy. Ciclesonide is overall non-genotoxic and non-carcinogenic. It has no teratogenicity in rats at up to 35 times the human dose, but did show teratogenicity in rabbits including fetal loss,

reduced fetal weight, cleft palate, skeletal abnormalities, and skin effects at less than the human nasal dose. Ciclesonide has a Pregnancy Category C listing.

Three new toxicology studies in juvenile rats and dogs were submitted with this NDA, but were not reviewed because they are not relevant to the proposed indication. See review by Dr. Luqi Pei for complete details.

## 5. Clinical Pharmacology/Biopharmaceutics

Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or des-CIC) following intranasal application. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid that is 120 times higher than the parent compound.

The clinical pharmacology program for CIC-HFA consists of four clinical trials, a relative bioavailability trial (M1-422) comparing to the two other marketed formulations of ciclesonide, a scintigraphy trial (060-101) evaluating local distribution, a PK/PD trial (M1-601), and an HPA axis trial (060-610). There was also an *in-vitro* drug-drug interaction study. See Table 1 modified from the primary Clinical Pharmacology review by Ying Fan, PhD for a summary of clinical pharmacology trials in the application.

**Table 1: Summary of clinical pharmacology trials**

Study #	N	Design	Dose	Duration	Description
M1-422	30 healthy (18-60 yrs)	R, OL, 3-way cross over	320 nasal aerosol 320 MDI inhalation 300 AQ nasal spray	SD	Relative BA study (PK)
060-101	10 healthy (18-65 yrs)	OL, fixed treatment sequence	160 nasal aerosol 200 nasal spray	SD	Scintigraphy study
M1-601	18 PAR 18 healthy (18-60 yrs)	R, DB, PC, 3-way cross over	320 nasal aerosol 160 nasal aerosol Placebo	2 wks	PK, PD (HPA axis), safety, tolerability
060-610	310 PAR (≥ 12 yrs)	MC, R, DB, PC, PG	160 nasal aerosol 320 nasal aerosol Placebo DX oral capsules DX placebo capsules	6 wks	HPA axis study
493/2007	Inhibition on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 (in vitro)				Drug-drug interaction study

R: randomized; OL: open label; DB: double blind; PC: placebo controlled; MC: multicenter; PG: parallel group; MDI: metered dose inhaler; SD: single dose; BA: bioavailability; PK: pharmacokinetic; PD: pharmacodynamic; HPA: hypothalamic-pituitary-adrenal; DX: dexamethasone, 6 mg QD 4 days

## 5.1. General considerations

### Relative bioavailability

The relative bioavailability of CIC-HFA compared to the other marketed ciclesonide formulations was evaluated in a randomized, open-label, single-dose, 3-period, crossover study (Study M1-422). Subjects (n=30) received 3 single-dose sequential treatments of ciclesonide 300 µg intranasal via aqueous nasal spray (Omnaris), 320 µg intranasal via HFA nasal aerosol (CIC-HFA), and ciclesonide 320 µg orally inhaled HFA metered dose inhaler (MDI; Alvesco). Results from this study demonstrated that CIC-HFA has much lower systemic exposure than Alvesco, approximately 10% of maximum exposure ( $C_{max}$ ) and 15% of overall exposure ( $AUC_{inf}$ ). Between nasal spray and nasal aerosol products, the mean  $C_{max}$  of Des-CIC was about four-fold higher with CIC-HFA relative to Omnaris. See Table 2.

These data have important implications for dose selection of CIC-HFA. The approved dose of Omnaris is 200 mcg once daily, while the proposed dose of CIC-HFA is 74 mcg once daily, approximately 2.7 fold lower. Given that the relative availability of CIC-HFA is four-fold higher than Omnaris, it is likely that patients treated with CIC-HFA will have higher serum levels of the active metabolite than patients treated with Omnaris.

**Table 2: Trial M1-422: Primary PK parameter estimates for Des-CIC in serum of healthy subjects for three different ciclesonide formulations**

Variable	Ciclesonide Aqueous Nasal Spray			Ciclesonide Nasal Aerosol		Ciclesonide Oral Inhalation	
	$C_{max}^{ab}$ (pg/mL) (LLOQ Values Set to No Value)	$C_{max}^a$ (pg/mL) (LLOQ Values Set to Zero)	$AUC_{0-\infty}^c$ (ng×hr/L)	$C_{max}$ (pg/mL)	$AUC_{0-\infty}$ (ng×hr/L)	$C_{max}$ (pg/mL)	$AUC_{0-\infty}$ (ng×hr/L)
N	5	29	0	29	18	29	29
Mean	15.20	2.62	NC <sup>d</sup>	59.09	397.5	586.2	2685
SD <sup>e</sup>	6.47	6.33	NC	22.62	128.0	180.8	644.3
Minimum	11.50	0.00	NC	21.80	175.8	332.0	1603
Median	12.40	0.00	NC	59.00	403.7	602.0	2762
Maximum	26.70	26.70	NC	111.0	684.3	1120	4301

<sup>a</sup> all available values included

<sup>b</sup>  $C_{max}$  = maximum (peak) serum drug concentration after regular administration of n doses

<sup>c</sup>  $AUC_{0-\infty}$  = area under the concentration-time curve from time of drug administration (time zero), extrapolated to infinity

<sup>d</sup> NC = not calculated

<sup>e</sup> SD = standard deviation

Taken from NDA 202-129, Module 2.72. Summary of Clinical Pharmacology Studies; Table 3, p.24

## Drug deposition

The deposition of ciclesonide was evaluated in Study 060-101. It was an open-label, single-dose, single-site, non-randomized study in 10 healthy male and non-pregnant, non-lactating female subjects between 18-65 years of age. Nasal inhalation of CIC-HFA resulted in deposition of almost the entire delivered dose in the nasal cavity (mean value of 98.36%) and negligible deposition in the lungs (mean value of 1.42%). Deposition of the delivered dose was minimal in the nasopharynx (mean value of 0.22%) or on the nasal wipes (mean value of 0.03%), and none of the dose was observed in the esophagus or stomach (swallowed). In contrast, for Omnaris, about 76% of the dose was deposited in the nasal cavity and about 23% was recovered in nasal wipes. See Table 3, taken from Dr. Fan's review, for a summary of results.

**Table 3: Trial 060-101: Initial deposition pattern as a percentage of delivered dose for CIC-HFA versus Omnaris**

	Nasal Cavity	Nasopharynx	Lungs	Swallowed	Nasal Wipes
<b>Nasal Aerosol</b>					
Mean (SD)	98.36 (1.09)	0.22 (0.14)	1.42 (1.02)	0.00	0.03 (0.067)
<b>Aqueous Nasal Spray (Omnaris)</b>					
Mean (SD)	76.38 (22.85)	0.34 (0.30)	0.55 (0.46)	0.00	22.74 (23.23)

These data suggest a potential mechanism for the increase in serum levels observed with CIC-HFA compared to Omnaris. Increased retention in the nose also may impact local safety of the product.

### Other pharmacokinetic information

Information regarding the absorption, distribution, metabolism, and elimination of ciclesonide is taken from the Alvesco and Omnaris programs, and the product label information regarding these parameters will apply to CIC-HFA. In brief, ciclesonide and des-ciclesonide both have negligible oral bioavailability due to low gastrointestinal absorption and high first-pass metabolism. Ciclesonide and des-ciclesonide are highly protein bound and are eliminated via biliary excretion. The plasma half life of ciclesonide is approximately 0.7 hours and des-ciclesonide is approximately 6-7 hours.

### 5.2. Drug-drug interactions

Drug-drug interaction trials performed with Alvesco demonstrated no interaction with oral erythromycin; ketoconazole increased des-ciclesonide 3.6 fold but not ciclesonide levels. Population studies demonstrated that albuterol and formoterol did not affect ciclesonide or des-ciclesonide PK.

In this NDA, human recombinant CYP (rCYP) enzymes were incubated with marker substrates in the presence or absence of ciclesonide (Study 493/2007) in order to evaluate ciclesonide as a direct inhibitor of CYP activity. The results indicated that there was little or no evidence of direct inhibition of human rCYP1A2, rCYP2A6, rCYP2B6, rCYP2C8, and rCYP2E1. However, because ciclesonide  $C_{max}$  following a single high dose (3  $\mu$ M) in asthmatic patients is around 6 nM, it is unlikely that there will be clinical CYP interactions from this perspective.

### 5.3. Intrinsic factors and special populations

Information regarding the absorption, distribution, metabolism, and elimination of ciclesonide is taken from the Alvesco and Omnaris programs, and the product label information regarding these parameters will apply to CIC-HFA. Population PK analysis showed that characteristics of des-ciclesonide after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject characteristics such as body weight, age, race, and gender. Studies in renally-impaired patients were not conducted since renal excretion of des-ciclesonide is a minor route of elimination. Compared with healthy subjects, the systemic exposure of des-ciclesonide

( $C_{max}$  and AUC) in patients with moderate to severe liver impairment increased in the range of 1.4 to 2.7 fold after 1280 mcg ex-actuator ciclesonide by oral inhalation. Dose adjustment in patients with liver impairment is not necessary.

### **5.5. QT assessment**

A QT assessment was not performed for this NDA, since ECG monitoring was performed in the Alvesco program.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical - Efficacy**

Safety and efficacy data for this application was taken from 4 clinical trials: a 2 week dose ranging trial in SAR (M1-602), two 2-week Phase 3 trials in SAR (060-622 and 060-634), and a 6 month Phase 3 trial in PAR (060-633). The primary efficacy endpoint for the PAR trial was at 6 weeks; it also had a 6 month open label extension period (060-635) giving a total duration of exposure of 12 months. All of the trials were conducted in adults and adolescents 12 years of age and older. The dose ranging trial was conducted during the spring allergy season (tree/grass) throughout the United States, the two Phase 3 SAR trials were conducted during the mountain cedar allergy season in Texas, and the PAR trial was conducted in patients throughout the United States with allergies to dust mite, cockroach, molds, or animal dander.

The primary endpoint for all four trials was the change from baseline in the average AM and PM reflective total nasal symptom scores (rTNSS). Secondary endpoints for all trials included the average AM and PM instantaneous nasal symptoms score (iTNSS) and the rhinoconjunctivitis quality of life questionnaire (RQLQ). The Phase 3 SAR trials also included the average AM and PM reflective total ocular symptom score (rTOSS) and the average AM and PM instantaneous total ocular symptom score (iTOSS) as secondary endpoints. TNSS is the sum of 4 symptom scores: runny nose, itchy nose, sneezing, and nasal congestion. TOSS is the sum of 3 symptom scores: itching, tearing, and redness. Each symptom is graded by the patient on a 4 point scale: 0=absent, 1=mild, 2=moderate, and 3=severe. Onset of nasal improvement was defined as the first assessment at which the iTNSS demonstrated a statistically significant improvement over placebo, and the onset of ocular improvement was defined as the first assessment at which the iTOSS demonstrated a statistically significant improvement over placebo. The RQLQ with standardized activities has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional), each of which is scored by the patient of a 7 point scale (0= not troubled to 6=extremely troubled).

Due to the clinical similarity between SAR and PAR, it is acceptable to have replicate trials in SAR and a single PAR trial to support both indications. See Table 4 for a summary of clinical efficacy and safety trials in the application.

**Table 4: Summary of clinical efficacy and safety trials**

Study	Objective	Design	Duration	Treatment Arms	Number of patients
<b>Phase 2b</b>					
M1-602	Dose range, safety, efficacy in SAR	MC, R, DB, PC	2 weeks	CIC-HFA 74 mcg	122
				CIC-HFA 148 mcg	125
				CIC-HFA 282 mcg	136
				Placebo HFA nasal	130
<b>Phase 3</b>					
060-622	Safety/efficacy in SAR	MC, R, DB, PC	2 weeks	CIC-HFA 74 mcg	237
				CIC-HFA 148 mcg	235
				Placebo HFA nasal	235
060-634	Safety/efficacy in SAR	MC, R, DB, PC	2 weeks	CIC-HFA 74 mcg	226
				CIC-HFA 148 mcg	225
				Placebo HFA nasal	220
060-633	Safety/efficacy in PAR	MC, R, DB, PC	6 weeks efficacy; 6 months safety	CIC-HFA 74 mcg	298
				CIC-HFA 148 mcg	505
				Placebo HFA nasal	307
060-635	Long-term safety (extension of 060-633)	OL	6 months	CIC-HFA 148 mcg	824

R=randomized, DB=double-blind, PC=placebo controlled, MC=multi-center, OL=open label, CO=cross-over

### **7.1. Dose selection**

Dose selection was based on knowledge from the Omnaris program confirmed with a dose ranging trial in SAR and evaluation of two doses in the Phase 3 trials. For Omnaris, the marketed dose 200 mcg once daily is efficacious, but doses of 100 mcg or lower did not demonstrate efficacy. Once daily dosing frequency was established in the Alvesco and Omnaris programs.

In the dose ranging trial, three doubling doses of CIC-HFA were tested: 74, 148, and 282 mcg, all of which demonstrated equal efficacy, suggesting that the doses are on the plateau of the dose-response curve. For the primary endpoint, the average AM and PM rTNSS, the treatment difference versus placebo was 0.66, 0.90, and 0.81 for the 74, 148, and 282 mcg dose groups, respectively, all of which were statistically significant. Given that there were no important differences between treatment groups, the two lowest doses were chosen for evaluation in the Phase 3 program.

As is discussed in Sections 7.2 and 7.3, no efficacy benefit of the higher 148 mcg dose over the 74 mcg dose was observed in the Phase 3 trials. Therefore, the sponsor is proposing the lower dose of 74 mcg once daily for approval, which is appropriate.

### **7.2. Seasonal allergic rhinitis**

The SAR claim is based on two replicative 2-week trials, 060-622 and 060-634. Both the 74 and 148 mcg doses demonstrated significant improvement for the primary endpoint and secondary nasal symptom endpoints, rTNSS and iTNSS, in both trials. The treatment benefit

of CIC-HFA for both doses was also consistently demonstrated in the individual rTNSS components. No added benefit is seen with the higher dose. These results are supportive of an indication for treatment of nasal symptoms of SAR. See Table 5, adapted from the statistical review by Dr. Qian Li.

**Table 5: Trials 060-622 and 060-634: TNSS efficacy results**

	Study 622						Study 634					
	Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg		Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
<b>rTNSS</b>												
Baseline	235	9.1	237	9.3	234	9.5	220	9.3	226	9.3	225	9.3
2-wk average	234	8.7	237	7.9	234	7.8	218	8.6	226	7.6	225	7.6
Diff from plb [CI]			0.9 [0.6,1.3]		1.1[0.7,1.5]				1.0[0.6,1.5]		1.0[0.6,1.5]	
p-value			<0.001		<0.001				<0.001		<0.001	
<b>iTNSS</b>												
Baseline	235	8.6	237	8.7	234	8.9	220	8.5	226	8.6	225	8.6
2-wk average	234	8.2	237	7.3	234	7.4	218	7.9	226	7.0	225	7.1
Diff from plb [CI]			0.9[0.5,1.3]		1.0[0.6,1.4]				0.9[0.5,1.3]		0.8[0.4,1.3]	
p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

RQLQ analysis was specified in the protocol to include only patients with a baseline score of  $\geq 3.0$ . Based on this analysis, RQLQ was statistically significant and also met the minimally clinically important difference (MCID) of 0.5 in both trials. However, because the trial was not stratified at baseline by RQLQ scores, an intention to treat (ITT) analysis of the entire population is the more relevant analysis. When Dr. Li analyzed RQLQ for the ITT population, the results were similar to the subgroup analysis. This suggests that improvement in RQLQ in SAR is a robust finding supportive of the sponsor's claim. No added benefit was seen with the higher dose. See Table 6, adapted from Dr. Li's review.

**Table 6: Trials 060-622 and 060-634: RQLQ efficacy results**

	Study 622						Study 634					
	Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg		Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
<b>RQLQ in patients with baseline RQLQ<math>\geq 3.0</math></b>												
Baseline	183	4.4	187	4.5	183	4.5	147	4.4	162	4.4	148	4.2
End of trtment	180	4.0	186	3.4	181	3.4	145	3.5	162	3.0	148	2.9
Diff from plb [CI]			0.6[0.4,0.9]		0.6[0.4,0.9]				0.6[0.3,0.9]		0.6[0.3,0.9]	
p-value			<0.001		<0.001				0.006			
<b>RQLQ in ITT population</b>												
Baseline	234	4.0	237	4.0	232	4.0	220	3.6	226	3.8	225	3.5
End of trtment	230	3.7	236	3.2	233	3.2	216	3.1	225	2.7	225	2.5
Diff from plb [CI]			0.6[0.4,0.8]		0.6[0.4,0.8]				0.5[0.3,0.8]		0.5[0.3,0.8]	
p-value			<0.001		<0.001				<0.001		<0.001	

CI – 95% 2-sided confidence interval

Similarly to RQLQ, the rTOSS analysis was specified in the protocol to include only patients with a baseline score of  $\geq 5.0$ . Based on this analysis, improvement in rTOSS compared to placebo was statistically significant in both treatment groups in Trial 060-622 but was only showed a significant difference for the 74 mcg treatment group in Trial 060-634. Because the trial was not stratified at baseline by rTOSS scores, an intention to treat analysis of the entire population is the more relevant analysis. When Dr. Li analyzed rTOSS for the ITT population, the results were similar to the subgroup analysis. The sponsor's subgroup analysis for iTOSS showed a benefit for both doses in both trials. Although the high dose group did not demonstrate statistical benefit for rTOSS in one trial, overall the totality of the data support benefit of CIC-HFA for the treatment of ocular symptoms of SAR. See Table 7, adapted from Dr. Li's review.

**Table 7: Trial 060-622 and 060-634: rTOSS efficacy results**

	Study 622				Study 634							
	Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg		Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg	
	N	Score	N	Score	N	Score	N	Score	N	Score	N	Score
<b>rTOSS in patients with baseline rTOSS<math>\geq 5.0</math></b>												
Baseline	148	7.0	164	6.9	160	7.0	165	7.0	159	7.1	161	7.0
2-wk average	147	6.5	164	5.8	160	5.9	164	6.1	159	5.7	161	5.8
Diff from plb [CI]			0.6[0.3,1.0]		0.6[0.3,1.0]				0.5[0.2,0.9]		0.3[-0.0,0.7]	
p-value			<0.001		<0.001				0.006		0.072	
<b>rTOSS in ITT population</b>												
Baseline	235	5.7	237	5.8	234	6.0	220	6.2	226	6.2	225	6.2
2-wk average	234	5.5	237	5.0	234	5.2	218	5.7	226	5.3	225	5.3
Diff from plb [CI]			0.5[0.3,0.8]		0.5[0.2,0.8]				0.4[0.1,0.7]		0.3[-0.0,0.6]	
p-value			<0.001		<0.001				0.024		0.055	

CI – 95% 2-sided confidence interval

Study 622 was designed to evaluate the onset of action at 4, 6, 8, 10, and 12 hours post-dose on Day 1 and 6 and 12 hours post-dose on Day 2 for iTNSS. Onset of nasal improvement as demonstrated by a statistically significant change compared to placebo was observed for both doses of CIC-HFA at 36 hours after the first dose. This statistically significant effect was observed again at 48 hours after the first dose and was maintained throughout the double-blind treatment period. The onset time was also confirmed in Study 634.

### **7.3. Perennial allergic rhinitis**

The PAR claim is based on 6 week data from a 6-month trial, 060-633. Both the 74 and 148 mcg doses demonstrated significant improvement for the primary endpoint and secondary nasal symptom endpoints, rTNSS and iTNSS, in both trials. The treatment benefit of CIC-HFA for both doses was also consistently demonstrated in the individual rTNSS components. No added benefit is seen with the higher dose. These results are supportive of an indication for treatment of nasal symptoms of PAR. See Table 8, adapted from the statistical review by Dr. Qian Li.

**Table 8: Trial 060-633: TNSS efficacy results**

	Placebo		CIC-HFA 74 mcg		CIC-HFA 148 mcg	
	N	Score	N	Score	N	Score
<b>rTNSS</b>						
Baseline	307	8.6	298	8.5	505	8.5
6-wk average	305	7.4	298	6.6	504	6.8
Diff from plb [CI]			0.7[0.4,1.0]		0.5[0.2,0.8]	
p-value			<0.001		<0.001	
<b>iTNSS</b>						
Baseline	307	7.7	298	7.7	505	7.6
6-wk average	305	6.6	298	6.0	504	6.1
Diff from plb [CI]			0.6[0.3,0.9]		0.4[0.1,0.7]	
p-value			<0.001		0.006	

CI – 95% 2-sided confidence interval

RQLQ analysis was specified in the protocol to include only patients with a baseline score of  $\geq 3.0$ . Based on this analysis, RQLQ demonstrated a statistically significant improvement over placebo for both doses, which met the clinically important difference of 0.5 only for the lower 74 mcg dose [0.6, 95% CI (0.3, 0.8) for 74 mcg, and 0.4, 95% CI (0.1, 0.6) for 148 mcg]. When RQLQ is analyzed for the entire population (intention-to-treat), neither dose meets the MCID (treatment difference of 0.3 for each dose), although a statistically significant difference from placebo was shown. These data do not support the sponsor's claim that CIC-HFA improves RQLQ in PAR. Ocular symptoms were not measured in this trial.

## 8. Safety

### 8.1. Overall safety

A total of 3,270 unique patients were included in the CIC-HFA clinical development program: 2,313 of whom received at least one dose of CIC-HFA nasal aerosol and 1,022 of whom received placebo nasal aerosol. The pooled safety database, which included the 4 Phase 2/3 SAR and PAR trials and the 6 week HPA axis trial included 967 placebo patients, 884 patients receiving 74 mcg, 1150 patients receiving 148 mcg, and 186 patients receiving 282 mcg of CIC-HFA. For safety reporting purposes, data were pooled into a short-term database (2-6 week trials and the first 6 weeks of trial 060-633) and a long-term database (6 month PAR trial 060-633). Demographics were typical of an allergic rhinitis patient population, with 63% females, 86% Caucasians, and a mean age of 38.5 years in the CIC-HFA groups overall. One-hundred-ninety eight patients who received CIC-HFA were adolescents in the 12-17 year old age group. The long-term exposure included 1110 patients, 307 of whom received placebo, 298 received CIC-HFA 74 mcg, and 505 received CIC-HFA 148 mcg.

For the CIC-HFA program, there were no deaths. There were a total of 6 serious adverse events (SAEs) in the short term safety database and 20 SAEs in the long-term safety database, which were evenly distributed across treatment groups. Other than 2 cases of pancreatitis in the placebo group, all were isolated events. Review of the SAEs does not demonstrate any concerning findings likely to be related to CIC-HFA.

The most common adverse events (AEs) reported in the short-term safety population were epistaxis, nasal/instillation site discomfort, upper respiratory tract infection, nasal septum disorder, oropharyngeal pain, and urinary tract infection. Of these, all occurred more frequently in the CIC-HFA groups compared to placebo. For the 6 month database, the most frequent AEs were URI, epistaxis, nasopharyngitis, sinusitis, and headache. These adverse events are generally common in the patient population. Events related to local nasal safety were explored in greater detail as described in Section 8.2 below.

## **8.2. Local safety**

In order to further evaluate local nasal safety, FDA requested that the sponsor re-classify local events into AE groupings rather than splitting into multiple preferred terms. These groups included non-ulcerative lesions (abrasions, excoriations, scabs and irritations), erosions and ulcerations, and other local nasal AEs. Nasal discomfort and instillation site discomfort were also grouped. In this review, adverse events are reported according to the reclassification rather than as submitted in the integrated summary of safety.

In the short term safety database using these groupings, nasal discomfort, non-ulcerative lesions, oropharyngeal pain and upper respiratory infection occurred more frequently in the 74 mcg dose group than placebo. For all ciclesonide groups, epistaxis, nasal abrasions, and nasal erosions also occurred more frequently. Epistaxis demonstrated a marked dose response. There was a statistically significant difference between placebo and the 282 mcg dose group for overall local adverse events and epistaxis. See Table 9 for a summary of local adverse events.

**Table 9: Local adverse events occurring in  $\geq 1\%$  of patients in any treatment group in the short-term (2-6 week) safety database (reclassification)**

Adverse event	Placebo (N=967)		74 mcg (N=884)		148 mcg (N=1150)		282 mcg (N=186)		Total CIC- HFA (N=2220)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All local AEs	124	(12.8)	123	(13.9)	165	(14.3)	36	(19.4)*	324	(14.6)
Epistaxis	27	(2.8)	26	(2.9)	40	(3.5)	14	(7.5)*	80	(3.6)
Nasal discomfort	17	(1.8)	28	(3.2)	33	(2.9)	4	(2.2)	65	(2.9)
Nasal Mucosal/Septum disorders	17	(1.8)	16	(1.8)	23	(2.0)	4	(2.2)	43	(1.9)
Non-ulcerative lesions	11	(1.1)	12	(1.4)	15	(1.3)	4	(2.2)	31	(1.4)
Irritation	10	(1.0)	11	(1.2)	8	(0.7)	2	(1.1)	21	(0.9)
Abrasion/excoriation/scabs	1	(0.1)	2	(0.2)	7	(0.6)	2	(1.1)	31	(1.4)
Erosions/ulcerations	5	(0.5)	4	(0.5)	6	(0.5)	0	0	10	(0.5)
Erosions	2	(0.2)	4	(0.5)	5	(0.4)	0	0	9	(0.4)
Ulcerations	3	(0.3)	0	0	1	(0.1)	0	0	1	(0.0)
Other <sup>†</sup>	1	(0.1)	0	0	2	(0.2)	0	0	2	(0.1)
Nasopharyngitis	15	(1.6)	4	(0.5)	12	(1.0)	5	(2.7)	21	(0.9)
Oropharyngeal pain	9	(0.9)	11	(1.2)	12	(1.0)	3	(1.6)	26	(1.2)
Sinusitis	12	(1.2)	7	(0.8)	12	(1.0)	0	0	19	(0.9)
Upper respiratory infection	8	(0.8)	15	(1.7)	21	(1.8)	2	(1.1)	38	(1.7)

<sup>†</sup> includes verbatim terms "cold sore right outer nares", "painful bump inside right nostril", and "sore right nares"

\* statistically significant difference from placebo

Data source: NDA 202-129 Document #0023, submitted 6 Dec 2011, Table 26.1a

The most concerning finding in the short-term database was the occurrence of two nasal septal perforations, both in the CIC-HFA 74 mcg group in two week SAR trials. One event occurred in the dose ranging trial (M1-602). The patient (5357/80294) had a remote history of nasal polyps, nasal septal perforation, and recurrence of nasal polyps post-surgery. She developed bilateral nasal septal erosions noted after one week of single blind placebo run-in, which should have excluded her from the trial, and had a nasal septal perforation noted after the two week treatment period. The second nasal septal perforation occurred in the Phase 3 SAR trial (060-634). The patient (0003/S150) was noted to have a "well healed" nasal septal perforation at the completion of the two week treatment period, without a perforation noted at baseline. Two months after the trial, an ENT physician reported that the lesion was sufficiently healed to be likely to have been present for months to years. Although in both cases the lesion may have pre-dated the trial, definitive proof is lacking, leaving the events to be possibly attributable to study drug.

For the long-term safety database, similar findings were observed, but differences from placebo for nasal discomfort and nasal mucosal lesions were more pronounced. Statistically significant differences from placebo were seen for both active treatment groups for nasal discomfort and for the 148 mcg treatment group for nasal mucosal lesions and abrasions. See

Table 10. No nasal septal perforations occurred in the 6 month trial. Data from the open label extension out to 12 months are consistent with the 6 month findings.

**Table 10: Local adverse events occurring in  $\geq 1\%$  of patients in any treatment group in the long-term (6 month) PAR trial 060-633 (reclassification)**

Adverse event	Placebo (N=307)		74 mcg (N=298)		148 mcg (N=505)		Total CIC-HFA (N=803)	
	n	(%)	n	(%)	n	(%)	n	(%)
All local AEs	118	(38.4)	126	(42.3)	219	(43.4)	345	(43.0)
Cough	8	(2.6)	9	(3.0)	19	(3.8)	28	(3.5)
Epistaxis	24	(7.8)	34	(11.4)	58	(11.5)	92	(11.5)
Nasal discomfort	2	(0.7)	17	(5.7)*	25	(5.0)*	42	(5.2)*
Nasal Mucosal/Septum disorders	9	(2.9)	11	(3.7)	30	(5.9)*	41	(5.1)
Non-ulcerative lesions	5	(1.6)	10	(3.4)	21	(4.2)*	31	(3.9)
Irritation	4	(1.3)	6	(2.0)	10	(2.0)	16	(2.0)
Abrasion/excoriation/scabs	1	(0.3)	5	(1.7)	12	(2.4)*	17	(2.1)
Erosions/ulcerations	4	(1.3)	2	(0.7)	8	(1.6)	10	(1.2)
Erosions	1	(0.3)	2	(0.7)	7	(1.4)	9	(1.1)
Ulcerations	3	(1.0)	0	0	1	(0.2)	1	(0.1)
Other <sup>†</sup>	1	(0.3)	0	0	1	(0.2)	1	(0.1)
Nasopharyngitis	21	(6.8)	18	(6.0)	33	(6.5)	51	(6.4)
Oropharyngeal pain	10	(3.3)	12	(4.0)	20	(4.0)	32	(4.0)
Pharyngitis streptococcal	5	(1.6)	7	(2.2)	5	(1.0)	12	(1.5)
Sinus headache	7	(2.3)	6	(2.0)	4	(0.8)	10	(1.2)
Sinusitis	17	(5.5)	14	(4.7)	28	(5.5)	42	(5.2)
Upper respiratory infection	29	(9.4)	43	(14.4)	65	(12.9)	108	(13.4)
Viral URI	5	(1.6)	11	(3.7)	11	(2.2)	22	(2.7)

<sup>†</sup> includes verbatim terms "painful bump inside right nose" and "sore right nare"; \*statistically significant difference from placebo  
Data source: NDA 202-129 Document #0023, submitted 6 Dec 2011, Table 26.2b

### 8.3. Hypothalamic-Pituitary-Adrenal (HPA) axis

Trial 060-610 is Phase 3, 6-week, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy trial designed primarily to evaluate the effects on the HPA axis by ciclesonide HFA nasal aerosol and Omnaris® Nasal Spray (referred to as ciclesonide AQ nasal spray in the study) when administered once daily to male and female subjects 12 years of age and older with a diagnosis of PAR. During the first 6 weeks, subjects received active treatment or placebo (HFA or placebo AQ). Beginning on study day 40 and ending on study day 43, subjects received double-blind treatment plus either placebo or active dexamethasone (6 mg). The primary endpoint was the change in serum cortisol AUC (0-24) from baseline to 6 weeks of treatment. There were no drug concentration measurements in this study. Compliance was verified through the use of video monitoring, subject self-reported study medication use, use of a dose indicator (HFA treatment groups only), and the results of the efficacy analyses.

In this trial, a significant change was observed in the positive control group (dexamethasone) for both the HFA and AQ portions of the trial. For CIC-HFA, there was no change in serum cortisol at twice the proposed to-be-marketed dose compared to placebo. A slight dose effect for CIC-HFA was seen that was not observed when corrected for baseline factors. See Table 11. For the ciclesonide aqueous nasal spray (Omnaris) at the marketed dose, a slight increase compared to placebo was observed that was not statistically significant. See Table 12. Given the wide confidence intervals in these trials, changes observed are unlikely to be of clinical importance and suggest that CIC-HFA and Omnaris at the proposed doses do not affect the HPA axis.

**Table 11: Change from baseline in serum cortisol AUC (0-24) ( $\mu\text{g}\cdot\text{h}/\text{dL}$ )-HFA treatment groups**

	Placebo HFA/ Dexamethasone 6 mg (n=18)	Placebo HFA/Placebo Dexamethasone (n=57)	Ciclesonide HFA 148 mcg (n=60)	Ciclesonide HFA 282 mcg (n=50)
<b>Baseline</b>				
Mean (SD)	167.7 (36.3)	173.1 (53.5)	171.7 (40.1)	183.2 (61.9)
<b>End of treatment</b>				
Mean (SD)			-1.5 (34.1)	-7.7 (33.7)
LS Mean (SE)	-154.4 (40)	-2.7 (41.1)	-2.6 (4.6)	-4.6 (5.0)
Diff Pbo LSM (95% CI)		-5.0 (4.6)	-2.4 (-15.1, 10.2)	-0.5 (-13.9, 13.0)

Data taken from CSR 060-610, Table 13, p. 102

Difference was calculated as placebo - ciclesonide. The change from baseline was analyzed using an analysis of covariance model (ANCOVA) with baseline, center, treatment, gender, and age as factors.

**Table 12: Change from baseline in serum cortisol AUC (0-24) ( $\mu\text{g}\cdot\text{h}/\text{dL}$ )-AQ treatment groups**

	Placebo AQ/ Dexamethasone 6 mg (n=18)	Placebo AQ/Placebo Dexamethasone (n=58)	Ciclesonide AQ 200 mcg (n=48)
<b>Baseline</b>			
Mean (SD)	183.0 (39.8)	179.0 (37.9)	172.8 (42.5)
<b>End of treatment</b>			
Mean (SD)			-8.0 (38.1)
LS Mean (SE)	-171.9 (39.5)	-0.2 (43.4)	-11.4 (5.7)
Diff Pbo LSM (95% CI)		-1.0 (5.2)	10.4 (-4.7, 25.5)

Data taken from CSR 060-610, Table 15, p. 106

Difference was calculated as placebo - ciclesonide. The change from baseline was analyzed using an analysis of covariance model (ANCOVA) with baseline, center, treatment, gender, and age as factors.

## 9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

## 10. Pediatrics

Adolescents aged 12 years and older were included in all of the pivotal trials for this application and in the HPA axis study. Typical of other allergic rhinitis programs, the proposed indication is down to age 12 years. The application was reviewed by the FDA

Pediatric Review Committee (PeRC) on November 30, 2011. The PeRC agreed to grant a partial waiver for children less than two years and a deferral in patients 2-11 years.

The lower age bound is typical for a nasal corticosteroid, and the Division has not asked that drugs of this class be studied in children younger than 2 years. The Division has historically taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (*J Allergy Clin Immunol* 2000, 106:832). For children younger than 2 years nasal corticosteroids is not an optimum choice because of possible nasal and systemic adverse effects. Such young patients are better treated with drugs of other classes such as antihistamines. Therefore, a waiver for patients under age 2 is appropriate.

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including nasal corticosteroids. A linear growth study was conducted for the Alvesco program. The trial was a 52-week, multi-center, double-blind, randomized, placebo-controlled parallel-group design that was conducted in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this study because compliance could not be assured. Ciclesonide blood levels were also not measured during the one-year treatment period. There was no difference in efficacy measures between the placebo and the ALVESCO groups. Because the systemic exposure is higher in the Alvesco program than with CIC-HFA, further linear growth trials are not needed.

The sponsor plans to investigate the safety and efficacy of CIC-HFA in 6-11 year olds and in 2-5 year olds sequentially, which is appropriate to assure safety in the younger age group. Because CIC-HFA 74 mcg appears to be on a plateau of the dosing curve and has higher systemic absorption and higher local nasal retention than Omnaris, lower doses will need to be investigated in the pediatric program.

## 11. Other Relevant Regulatory Issues

### 11.1. Ethics and data integrity

For the pivotal trials submitted in this application, two investigators reported payments from the sponsor outside the clinical trials in excess of \$25,000. One investigator participated only in the (b) (6) trial, enrolling (b) (6) patients; this site was not audited because it was deemed that potential bias for these patients would have been unlikely to affect the results and the trial did not form the basis of the efficacy decision. The other investigator (b) (6) was audited by the sponsor (b) (6)

Therefore, the site was not audited because a further FDA audit was deemed to be unlikely to change the results of the action.

Given the safety findings of nasal septal perforations, the Division of Scientific Investigators (DSI) was consulted to conduct site inspections at the two sites where these adverse events were reported. Dr. Robert Lee Jacobs was a high enroller in all three Phase 3 trials (060-622, 060-634, and 060-633). Dr. Pinkus Goldberg participated in the dose ranging and PAR trials (M1-602, 060-633). The auditor did not identify any significant GCP or scientific integrity issues at these sites; however, one of the patients with a nasal septal perforation was identified as a protocol violation as she was enrolled in the presence of nasal erosions. The sponsor also identified this issue as a protocol violation.

### **11.2. Proprietary name review**

DPARP consulted the Division of Medication Error Prevention and Analysis (DMEPA) to conduct a review of proprietary names the sponsor proposed for CIC-HFA. As of the date of this review, the proprietary name is still under discussion with the sponsor. (b) (4)  
[REDACTED] were deemed unacceptable [REDACTED] (b) (4)

## **12. Labeling**

Nycomed has submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products in this class. The label was reviewed by appropriate disciplines of this Division in addition to consults by the Office of Prescription Drug Promotion (OPDP), the Division of Medication Error Prevention and Analysis (DMEPA), and the Division of Medical Policy Programs (DMPP). Additional language will be added to the label to warn physicians and patients of the risk of nasal perforations observed in clinical trials with CIC-HFA. Information will be added to the patient instructions for use to instruct patients on how to reinsert the canister if the inhaler is dropped. Additional changes to improve accuracy and consistency will also be added. As of the date of this review, labeling discussions with the sponsor are ongoing.

## **13. Recommendations/Risk Benefit Assessment**

### **13.1. Recommended regulatory action**

The recommended regulatory action for this application is approval for the indication "treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older."

### **13.2. Risk benefit assessment**

CIC-HFA has demonstrated robust efficacy for both SAR and PAR indications; however, the occurrence of two nasal perforations in the 2-week trials of the clinical program is concerning for the local safety of the product. While nasal septal perforations are a known adverse event with nasal steroid products, events are rare, and typically seen only in post-marketing trials. The known increased retention in the nose and increased systemic availability compared to

Omnaris suggest that local safety may be influenced by higher local drug levels, while lack of findings in the placebo group suggest that these events are not due to a formulation effect.

The following factors mitigate but do not negate the finding of nasal septal perforations: 1) the septal perforations occurred in patients with a history of nasal pathology, 2) septal perforations were not observed in long term trials, and 3) septal perforations were not observed in patients receiving doses higher than the to-be-marketed dose. Given these mitigating factors, the robust efficacy of the product, and the known class effect of nasal steroids, approval is recommended. However, because some degree of uncertainty exists as to the degree of risk of local nasal and ocular events compared to other marketed products, we recommend a post-marketing safety trial comparing CIC-HFA to Omnaris to evaluate this risk.

### ***13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies***

A Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

### ***13.4. Recommendation for other Postmarketing Requirements and Commitments***

There are recommendations for one post-marketing requirement (PMR) and one post-marketing commitment (PMC). The PMR is for a trial to evaluate local safety of CIC-HFA and the PMC is to improve the robustness of the inhaler design.

- Conduct a randomized clinical trial in patients with perennial allergic rhinitis of minimum 6 months duration to evaluate local and ocular safety with ciclesonide HFA. Include the active comparator, Omnaris, with a minimum of 300 completers per treatment group. Allow for a broad patient population similar to real-world use, including patients with a history of nasal pathology or nasal surgery. Safety assessments should include blinded nasal and ocular examinations.
- Improve the device robustness or redesign the actuator to address the observed separation of actuator from canister and observed overcounting of the dose counter on drop testing from a height of 1 meter. Your final report submission should include the redesign information and drop testing results with the redesigned drug product. Submit the final report per the classification provided in the comparability protocol based on risk (e.g., PAS, CBE 30, CBE, 0).

### ***13.5. Recommended comments to applicant***

There are no recommended comments to the applicant outside of the PMC and PMR studies.

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THERESA M MICHELE  
12/23/2011