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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	January 20, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-2129
Applicant Name:	Sunovion Pharmaceuticals, Inc., for Nycomed
Date of Submission:	March 19, 2011
PDUFA Goal Date:	January 21, 2012
Proprietary Name:	Zetonna Nasal Aerosol
Established Name:	Ciclesonide Nasal Aerosol
Dosage form:	Nasal Spray
Strength:	37 mcg ciclesonide ex actuator (50 mcg ex valve) per actuation of 50 microliter metered volume
Proposed Indications:	Treatment of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis in patients 12 years of age and older
Action:	Approval

1. Introduction

Sunovion Pharmaceuticals submitted this 505(b)(1) application for use of Zetonna Nasal Aerosol (ciclesonide nasal aerosol, HFA propelled) for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. The proposed dose is 1 actuation per nostril once daily (37 mcg ex actuator per actuation). The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are many drugs approved for use in patients with allergic rhinitis (AR) that include oral and intranasal H1 antihistamines, intranasal corticosteroids, and the oral leukotriene receptor antagonist montelukast. There are various intranasal corticosteroids marketed for the treatment of AR in the United States. Ciclesonide is a corticosteroid and is currently marketed in the United States as two formulations, an inhalation aerosol formulated as a solution containing the propellant HFA-134a and ethanol delivered via a metered-dose inhaler (MDI) for the treatment of asthma (marketed as Alvesco), and a nasal spray in an aqueous suspension delivered via a pump spray for the treatment of nasal symptoms of SAR and PAR (marketed as Omnaris Nasal Spray). The current application proposes to expand the available intranasal corticosteroid treatment options for AR. The proposed Zetonna Nasal Aerosol product utilizes the MDI canister from Alvesco, which is coupled with a new nasal actuator to allow for nasal administration of the existing MDI formulation.

All intranasal corticosteroids currently available in the US for the treatment of AR are aqueous-based and are often associated with back-of-the-throat run off or post-nasal drip. In the past there were CFC-based intranasal corticosteroid aerosol products, but these are not currently available because of the phase-out of CFCs. Zetonna Nasal Aerosol is proposed to provide a non-CFC based intranasal corticosteroid aerosol treatment option for patients with AR.

3. Chemistry, Manufacturing, and Controls

The drug substance ciclesonide is a known compound that is already approved in commercial inhalation and nasal spray products as mentioned above. Zetonna Nasal Aerosol is a pressurized metered dose aerosol canister containing a solution formulation of ciclesonide with (b) (4) ethanol and (b) (4) HFA-134a (same as that used in Alvesco as described above), and fitted with a nasal actuator with a 0.5 mm exit orifice. The product has an integrated dose counter. Zetonna Nasal Aerosol delivers 37-mcg ciclesonide from the actuator (50 mcg from the valve) in 50 microliters (59.3 mg) per actuation. The commercial presentation provides 60 actuations after priming and has a net fill weight of 6.1 gm. There will be a post-marketing commitment to improve the ruggedness of the product because the assembled inhaler comes apart relatively easily (e.g., on drop test) and the dose counter can give false readings after dropping. These are not approvability issues or post-marketing requirements because the product functions properly on reassembly and a dose-counter is not critical for a nasal spray product.

The drug substance is manufactured (b) (4) in a facility (b) (4) The finished dosage form is manufactured at a (b) (4) facility (b) (4) (b) (4) facilities in (b) (4) are responsible for microbial testing, and for release and stability testing. All manufacturing and testing facilities associated with this application have acceptable EER status. The submitted stability data support storing at room temperature and an expiry of 24 months.

4. Nonclinical Pharmacology and Toxicology

A full toxicology assessment for ciclesonide was submitted previously and reviewed under the NDAs for Alvesco and Omnaris and was found to be acceptable. No new preclinical data were submitted with this application. Also, the previously submitted toxicity studies did not identify any local effects of the to-be-marketed formulation on nasal cavity in animals.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for ciclesonide hydrochloride were addressed in the original NDAs for Alvesco and Omnaris Nasal Spray.

Ciclesonide is a pro-drug that is hydrolyzed by esterases to a biologically active metabolite des-ciclesonide or RM1. Des-ciclesonide has approximately a 120-fold greater affinity for the glucocorticoid receptor than the parent drug ciclesonide. Ciclesonide and des-ciclesonide have less than 1% oral bioavailability due to low gastrointestinal absorption and high first-pass metabolism. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by CYP3A4 and to a lesser extent by CYP2D6. The intranasal administration of ciclesonide at the recommended dose results in negligible serum concentration of ciclesonide; however, the active metabolite des-ciclesonide is detected in the serum of some patients.

Sunovion conducted two studies in adults to assess relative bioavailability of Zetonna Nasal Aerosol compared to approved products containing ciclesonide. In a single dose study involving 30 healthy volunteers (study 422), des-ciclesonide exposure was approximately 90% lower (Cmax) from Zetonna Nasal Aerosol 320 mcg (ex-valve) compared to Alvesco 320 mcg (ex-valve), and approximately 4 fold higher (Cmax) from Zetonna Nasal Aerosol 320 mcg (ex-valve) compared to Omnaris Nasal Spray 300 mcg (ex-actuator). In a single dose study involving 10 healthy volunteers (study 101), nasal cavity deposition of ciclesonide assessed by scintigraphy was approximately 98% for Zetonna Nasal Aerosol compared to approximately 76% for Omnaris Nasal Spray. These two studies suggest that systemic exposure and local nasal delivery and retention from Zetonna Nasal Aerosol are higher compared to approved Omnaris Nasal Spray.

Sunovion conducted a 6-week HPA axis assessment study in patients 12-73 years of age with PAR (study 610). The study included two Zetonna Nasal Aerosol doses of 148 mcg and 282 mcg (ex-actuator dose), placebo, and dexamethasone oral capsule treatment (for the last 4 days) arm as a positive control. The difference from placebo for change from baseline in serum cortisol AUC (0-24 hr) levels at end of treatment were -2.4 microgram-hr/dL, -0.5 microgram-hr/dL, and -148.3 microgram-hr/dL, for Zetonna Nasal Aerosol 148 mcg, Zetonna Nasal Aerosol 282 mcg, and dexamethasone treatment arms.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application was typical of an AR program covering both the SAR and PAR indications. Some characteristics of the studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies

ID Year *	**Study type**	**Study duration**	**Patient Age, yr**	**Treatment groups#**	**N (ITT)**	**Primary efficacy variable**	**Countries**
602 2007	Dose ranging, in SAR	2 week	12 - 76	Cicl HFA 74 mcg QD Cicl HFA 148 mcg QD Cicl HFA 282 mcg QD Placebo	122 125 136 130	Reflective total nasal symptom score over 2 wks	US [Various States]
622 2009	Efficacy and Safety in SAR	2 week	12 - 72	Cicl HFA 74 mcg QD Cicl HFA 148 mcg QD Placebo	237 235 235	Reflective total nasal symptom score over 2 wks	US [Texas]
634 2010	Efficacy and Safety in SAR	2 week	12 - 81	Cicl HFA 74 mcg QD Cicl HFA 148 mcg QD Placebo	226 225 220	Reflective total nasal symptom score over 2 wks	US [Texas]
633 2010	Efficacy and Safety in PAR	6 month	12 - 78	Cicl HFA 74 mcg QD Cicl HFA 148 mcg QD Placebo	298 504 307	Reflective total nasal symptom score over 6 wks	US [Various States]
635 2011	Safety, extension of 633	6 month	12 - 79	Cicl HFA 148 mcg QD	824		US

*Year study subject enrollment ended
Cilc = ciclesonide HFA Nasal aerosol administered in each nostril (37 mcg/actuation);
Note: All doses are ex-actuator (end of the actuator from where the drug is delivered to patients)

b. Design and conduct of the studies

All efficacy and safety studies (602, 622, 634, and 633) were randomized, double-blind, placebo-controlled, parallel-group design study conducted in patients 12 years of age and older with SAR or PAR. For the SAR studies 622 and 634 the allergen was specified as Texas Mountain Cedar. The studies had a 1-3 week single-blind placebo run-in period followed by double-blind treatment period of 2 weeks for SAR studies 602, 622, and 634, and 6 months for PAR study 633 (Table 1). The primary efficacy endpoint for all studies was the change from baseline in average morning and evening reflective total nasal symptom scores (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) collected daily averaged over 2 weeks of treatment for SAR studies or 6 weeks of treatment for the PAR study (Table 1). Some key secondary efficacy variables included: (1) the instantaneous recording of the same four symptoms (iTNSS) for all studies, (2) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for SAR studies 622 and 634 and PAR study 633 of patients with impaired quality of life defined as RQLQ score >3 during the run-in period, and (3) reflective and instantaneous total ocular symptom score (rTOSS or iTOSS: sum of ocular itching, tearing, and redness; each scored on 0-3 scale) for SAR studies 622 and 634 of symptomatic patients defined as TOSS of >5 during the run-in period. Safety assessments included recording of adverse events, vital signs, physical examinations including ENT examinations, and clinical laboratory measurements.

Study 635 was an open label safety extension study of the PAR study 633. At the end of 6 months double-blind treatment in study 633, all patients were screened and eligible patients were treated with ciclesonide for 6 more months. Safety assessments included

recording of adverse events, vital signs, physical examinations including ENT examinations, and clinical laboratory measurements.

The design and conduct of efficacy and safety studies were typical of an AR program with some deviations. First, in the SAR studies 622 and 634 the allergen was specified as Texas Mountain Cedar. This is acceptable because demonstration of efficacy in one allergen sensitive SAR patient group is expected to support efficacy in other allergen sensitive patient groups in SAR because the underlying pathophysiology of SAR is similar across allergens. Texas Mountain Cedar produces intense symptoms and clinical studies conducted in SAR patients allergic to this allergen may show a larger treatment effect size compared to clinical studies conducted in SAR patients allergic to heterogeneous seasonal allergens. Nevertheless, Texas Mountain Cedar is an acceptable model to study SAR. Second, for the key secondary efficacy variables of RQLQ and TOSS only patients with high baseline scores were included. This is not acceptable because such analyses do not represent the whole SAR population and conclusions from such analyses cannot be generalized to support labeling claims. In this review, results from only the whole group will be shown.

c. Efficacy findings and conclusions

The submitted studies support efficacy of Zetonna Nasal Aerosol at a dose of 74 mcg (37 mcg in each nostril) administered once daily in adult and adolescent patients with SAR and PAR 12 years of age and older.

In the dose ranging study (602), a clear dose-related increase in efficacy was not observed, which is not unexpected for a nasal corticosteroid. All doses of Zetonna Nasal Aerosol demonstrated a statistically significant difference from placebo in the change from baseline rTNSS and iTNSS with no clear numerical trend (Table 2). Sunovion selected the lowest two doses for further studies to confirm efficacy in two SAR and one PAR studies. In all of these studies the 74 mcg and 148 once daily doses were statistically superior to placebo in the primary efficacy endpoint of rTNSS and also iTNSS with no clear separation between the two doses (Table 2). The four individual symptom scores of the TNSS contributed to the composite score in the Zetonna Nasal Aerosol treatment groups (data not shown in this review). Sunovion is proposing the lower of the two doses, 74 mcg once daily, as the recommended dose, which is reasonable and supported by the data.

Sunovion included the RQLQ in the confirmatory SAR and PAR studies to support labeling claim. The RQLQ is a 28-item disease specific (allergic rhinitis) quality of life instrument with seven domains (activity limitations, sleep problems, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function). Patients treated with Zetonna Nasal Aerosol demonstrated statistically significant improvements in RQLQ compared to placebo in both SAR studies and the PAR study (Table 3). The treatment group differences in each of the SAR studies crossed 0.5, which is considered to be the MID (minimum important difference), but not in the PAR study. The labeling claim for RQLQ is supported for patients with SAR but not for patients with PAR.

Sunovion analyzed ocular symptoms in the confirmatory SAR studies to support a labeling claim. Patients treated with Zetonna Nasal Aerosol demonstrated statistically significant improvements in rTOSS compared to placebo (Table 4). The improvement in rTOSS in the SAR studies supports the effectiveness of Zetonna Nasal Aerosol in treating eye symptoms in patients with SAR but not in patients with PAR.

Table 2. Change from baseline in nasal symptoms scores rTNSS and iTNSS *

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from placebo LS mean	95% CI	P value
SAR Trial 602							
rTNSS	Cicl HFA 74 mcg QD	122	9.45	-1.98	0.66	0.16, 1.16	0.010
	Cicl HFA 148 mcg QD	125	9.02	-2.21	0.90	0.40, 1.39	<0.001
	Cicl HFA 282 mcg QD	136	9.20	-2.12	0.81	0.32, 1.29	0.001
	Placebo	129	9.02	-1.32			
iTNSS	Cicl HFA 74 mcg QD	153	8.39	-1.89	0.75	0.25, 1.25	0.003
	Cicl HFA 148 mcg QD	158	7.96	-2.00	0.86	0.36, 1.36	<0.001
	Cicl HFA 282 mcg QD	153	8.16	-1.89	0.75	0.26, 1.23	0.002
	Placebo	153	8.10	-1.14			
SAR Trial 622							
rTNSS	Cicl HFA 74 mcg QD	237	9.32	-1.45	0.94	0.57, 1.32	<0.0001
	Cicl HFA 148 mcg QD	234	9.46	-1.59	1.08	0.70, 1.45	<0.0001
	Placebo	234	9.10	-0.51			
iTNSS	Cicl HFA 74 mcg QD	237	8.68	-1.34	0.87	0.50, 1.25	<0.0001
	Cicl HFA 148 mcg QD	234	8.94	-1.47	1.00	0.63, 1.37	<0.0001
	Placebo	234	8.61	-0.47			
SAR Trial 634							
rTNSS	Cicl HFA 74 mcg QD	226	9.34	-1.75	1.04	0.61, 1.46	<0.0001
	Cicl HFA 148 mcg QD	225	9.26	-1.74	1.02	0.59, 1.45	<0.0001
	Placebo	218	9.28	-0.72			
iTNSS	Cicl HFA 74 mcg QD	226	8.60	-1.58	-0.90	0.49, 1.32	<0.001
	Cicl HFA 148 mcg QD	225	8.64	-1.51	-0.83	0.42, 1.25	<0.001
	Placebo	218	8.53	-0.68			
PAR Trial 633							
rTNSS	Cicl HFA 74 mcg QD	298	8.53	-1.97	0.69	0.35, 1.04	0.0001
	Cicl HFA 148 mcg QD	504	8.50	-1.82	0.54	0.24, 0.84	0.001
	Placebo	305	8.62	-1.28			
iTNSS	Cicl HFA 74 mcg QD	298	7.66	-1.77	0.58	0.25, 0.92	0.001
	Cicl HFA 148 mcg QD	504	7.64	-1.60	0.42	0.12, 0.72	0.012
	Placebo	307	7.70	-1.18			

* Subject-rated rated AM and PM reflective or instantaneous total nasal symptom scores (rTNSS or iTNSS) (maximum score = 24) averaged over the 2-week treatment period in SAR and the first 6-week treatment period in PAR studies.
† Cicl = ciclesonide HFA Nasal aerosol administered in each nostril (37 mcg/actuation; ex-actuator dose)

Table 3. Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) in the pivotal SAR and PAR studies

	Treatments †	n	Baseline LS mean	End of treatmnet	Difference from placebo LS mean	95% CI	P value
SAR study 622							
RQLQ	Cicl HFA 74 mcg QD	237	4.0	3.2	0.6	0.4, 0.8	<0.001
	Cicl HFA 148 mcg QD	232	4.0	3.2	0.6	0.4, 0.8	<0.001
	Placebo	234	4.0	3.7			

	Treatments †	n	Baseline LS mean	End of treatmnet	Difference from placebo LS mean	95% CI	P value
SAR study 634							
RQLQ	Cicl HFA 74 mcg QD	226	3.8	2.7	0.5	0.3, 0.8	<0.001
	Cicl HFA 148 mcg QD	225	3.5	2.5	0.5	0.3, 0.5	<0.001
	Placebo	220	3.6	3.1			
PAR study 633							
RQLQ	Cicl HFA 74 mcg QD	298	3.1	2.1	0.3	0.1, 0.5	0.002
	Cicl HFA 148 mcg QD	505	3.1	2.1	0.3	0.1, 0.4	0.002
	Placebo	305	3.2	2.4			

† Cilc = ciclesonide HFA Nasal aerosol administered as 1 actuation in each nostril (37 mcg/actuation; ex-actuator dose)

Table 4. Change from baseline in reflective ocular total symptom scores (rTOSS) in two SAR studies

	Treatments †	n	Baseline LS mean	Average over 2-week period	Difference from placebo LS mean	95% CI	P value
SAR study 622							
rTOSS	Cicl HFA 74 mcg QD	237	5.8	5.0	0.5	0.3, 0.8	<0.001
	Cicl HFA 148 mcg QD	234	6.0	5.2	0.5	0.2, 0.8	<0.001
	Placebo	235	5.7	5.5			
SAR study 634							
rTOSS	Cicl HFA 74 mcg QD	226	6.2	5.3	0.4	0.1, 0.7	0.024
	Cicl HFA 148 mcg QD	225	6.2	5.3	0.3	-0.0, 0.6	0.055
	Placebo	220	6.2	5.7			

† Cicl = ciclesonide HFA Nasal aerosol administered in each nostril (37 mcg/actuation; ex-actuator dose)
Note: All doses are ex-actuator (end of the actuator from where the drug is delivered to patients)

To support onset of action claim, Sunovion did not conduct dedicated studies such as an "allergen chamber" study or "day-in-the-park" study that provides pharmacodynamics onset of action. Instead, onset of action for Zetonna Nasal Aerosol was assessment by frequent recording of iTNSS in the pivotal SAR and PAR studies after the first dose. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment and placebo in the efficacy measure is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful. The pivotal SAR and PAR studies provide more clinically meaningful onset of action information than the pharmacodynamics "allergen chamber" and "day-in-the-park" type studies. The data submitted support onset of action of 36 hours for Zetonna Nasal Aerosol.

8. Safety

a. Safety database

The safety assessment of Zetonna Nasal Aerosol is primarily based on studies listed in Table 1. The overall safety database was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Zetonna Nasal Aerosol in patients 12 years of age and older. There were no deaths in the clinical program. Serious adverse events

were few, did not appear to be related to ciclesonide, and did not suggest a new safety signal. Common adverse events in Zetonna Nasal Aerosol treated patients in decreasing frequency were epistaxis, headache, upper respiratory infection, instillation site discomfort, and nasal discomfort.

Nasal septum perforation was reported in 2 patients, both in the Zetonna Nasal Aerosol 74 mcg treatment group, and both in 2-week SAR studies. One perforation occurred in a 58 year female enrolled in study 602. The patient had nasal turbinate inflammation at screening, bilateral septum erosions at the end of single-blind placebo run-in period, and at the end of double-blind treatment period (day 16) was noted to have nasal septum perforation. The investigator concluded that the perforation was likely related to study medication. Later evaluation identified that the patient had nasal septum perforation and surgery for nasal polyps approximately 10 years previously. The second perforation occurred in a 34 year old female enrolled in study 634. The patient was noted to have normal examination at screening. A nasal septum perforation was noted towards the end of double-blind treatment period (day 13). An independent ENT examination done approximately 2 months later concluded that the perforation could have been there before treatment. Later evaluation identified that this patient had septum rhinoplasty surgery approximately 20 years previously.

Nasal septum perforation is a known safety signal for nasal corticosteroids, but is typically seen in the post-marketing setting, and is not common in NDA studies. The two perforations seen the Zetonna Nasal Aerosol clinical program occurred in the short-term studies, in the lowest ciclesonide dose treatment groups, and one had confounding factors of prior history of nasal septum diseases. Nevertheless, these two perforations cannot be ignored, because these occurred during randomized treatment periods with equal possibility of patients with similar confounding factors in the placebo treatment arms who did not have nasal septum perforation.

Nasal ulcers are often precursors of nasal septum perforations. In the Zetonna Nasal Aerosol program nasal ulcer findings did not correlate with nasal septum perforations. In the program nasal ulcers were identified in 4 patients, 1 in the ciclesonide 148 mcg group, and 3 in the placebo group.

Selected local nasal adverse reactions that occurred commonly are shown in Table 5 and Table 6. More patients in the Zetonna Nasal Aerosol treatment groups had local nasal adverse reactions and some discontinued from studies because of local nasal adverse reactions. These findings suggest local nasal irritating potential for Zetonna Nasal Aerosol. The frequency difference from placebo for these findings were not large and generally within ranges seen in other nasal corticosteroid studies.

The local nasal findings described above suggest somewhat high local nasal irritation potential for Zetonna Nasal Aerosol, which is not qualitatively different from other nasal corticosteroids. To better define the frequency of local nasal adverse reactions for Zetonna Nasal Aerosol, Sunovion will conduct a post-marketing safety study comparing Zetonna Nasal Aerosol to an active nasal corticosteroid (the currently marketed Omnaris

Nasal Spray aqueous formulation). Findings of interest will be those described in Tables 5 and 6, and nasal septum perforations, if they occur. The result of such a safety study will help inform health care providers to better balance the possible efficacy advantage of Zetonna Nasal Aerosol to the possible safety disadvantage while deciding to prescribe Zetonna Nasal Aerosol.

Table 5. Selected common adverse reactions (occurring at least in 1% of patients in any treatment group) and these adverse reactions that resulted in patient discontinuations from studies, from SAR and PAR studies 2-6 weeks in duration *

	Placebo	Ciclesonide Nasal Aerosol		
		74 mcg	148mcg	282 mcg
	n=967 n (%)	n=884 n (%)	n=1150 n (%)	n=186 n (%)
Adverse Reactions:				
Epistaxis including blood tinged mucous	27 (2.8%)	26 (2.9%)	40 (3.5%)	14 (7.5%)
Nasal discomfort	12 (1.2%)	13 (1.5%)	18 (1.6%)	2 (1.2%)
Nasal septum disorder	7 (0.7%)	9 (1.0%)	14 (1.2%)	3 (1.6%)
Nasal mucosal disorder	7 (0.7%)	8 (0.9%)	9 (0.8%)	1 (0.5%)
Instillation site discomfort	5 (0.5%)	16 (1.8%)	16 (1.4%)	2 (1.1%)
Upper respiratory tract infection	8 (0.8%)	15 (1.7%)	21 (1.8%)	2 (1.1%)
Adverse Reactions Causing Discontinuations:				
Epistaxis including blood tinged mucous	1 (0.1%)	0	1 (0.1%)	0
Nasal discomfort	0	0	0	1 (0.5%)
Nasal septum disorder	0	0	2 (0.2%)	0
Nasal mucosal disorder	0	0	0	0
Nasal dryness (not in AR above)	0	1 (0.1%)	1 (0.1%)	0
Instillation site discomfort	0	1 (0.1%)	0	0
Upper respiratory tract infection	0	0	0	0

* Source: Applicant's Summary of Safety – Table 14, and Table 18

Table 6. Selected common adverse reactions (occurring at least in 1% of patients in any treatment group) and these adverse reactions that resulted in patient discontinuations from studies, from PAR study (633) 6 months in duration *

	Placebo	Ciclesonide Nasal Aerosol		
		74 mcg	148mcg	282 mcg
	n=307 n (%)	n=298 n (%)	n=505 n (%)	n=000 n (%)
Adverse Reactions:				
Epistaxis including blood tinged mucous	24 (7.8%)	34 (11.4%)	57 (11.3%)	-
Nasal discomfort	2 (0.7%)	8 (2.7%)	15 (3.0%)	-
Nasal septum disorder	3 (1.0%)	6 (1.7%)	16 (3.2%)	-
Nasal mucosal disorder	3 (1.0%)	8 (2.7%)	14 (2.8%)	-
Instillation site discomfort	0	10 (3.4%)	9 (1.8%)	-
Upper respiratory tract infection	29 (9.4%)	43 (14.4%)	65 (12.9%)	-
Adverse Reactions Causing Discontinuations:				
Epistaxis including blood tinged mucous	1 (0.3%)	2 (0.7%)	2 (0.4%)	-
Nasal discomfort	0	0	0	-
Nasal septum disorder	0	0	2 (0.4%)	
Nasal mucosal disorder	0	0	3 (0.6%)	-
Nasal dryness (not in AR above)	0	1 (0.3%)	1 (0.2)	-
Instillation site discomfort	0	1 (0.3%)	0	-
Upper respiratory tract infection	0	1 (0.3%)	0	-

	Placebo	Ciclesonide Nasal Aerosol		
		74 mcg	148mcg	282 mcg
	n=307	n=298	n=505	n=000
	n (%)	n (%)	n (%)	n (%)
* Source: Applicant's Summary of Safety – Table 15, and Table 19				

Ophthalmologic examination was not done in the Zetonna Nasal Aerosol program. During the pre-IND meeting with the Division in 2006, it was agreed that detailed ophthalmologic examination would not be necessary because extensive ophthalmologic data were collected in the Omnaris Nasal Spray and Alvesco programs. Detailed ophthalmologic data were collected in those programs because there were concerns with lens opacification seen in one study with the ciclesonide inhalation formulation. Ophthalmologic data from the Omnaris Nasal Spray and Alvesco programs were generally negative. The Zetonna Nasal Aerosol program did not identify any ocular safety issues. There were no spontaneous reports of glaucoma, cataracts, or visual disturbances. Although there were no spontaneous reported ocular safety signals for Zetonna Nasal Aerosol, but the prior assumptions of safety is somewhat less relevant because the systemic exposure and local nasal delivery and retention from Zetonna Nasal Aerosol are now known to be higher compared to approved Omnaris Nasal Spray (see Section 5 above). Sunovion will be asked to assess ocular safety in the post-marketing safety study that will be conducted to assess local nasal safety of Zetonna Nasal Aerosol (see the paragraph above).

HPA axis effect was assessed in patients 12-73 years of age with PAR (results described in Section 5 above). Sunovion may need to conduct a further HPA axis study in pediatric patients as the pediatric program is conducted for patients below 12 years of age because systemic exposure and local nasal delivery and retention from Zetonna Nasal Aerosol are higher compared to approved Omnaris Nasal Spray.

A linear growth study with Zetonna Nasal Aerosol is not necessary because a growth study has been conducted with Alvesco. Systemic exposure from Zetonna Nasal Aerosol is lower compared to Alvesco (see Section 5 above). The Division does not require a separate growth study for the same active moiety when linear growth data are available with a different formulation for the same active moiety with higher exposure.

c. REMS/RiskMAP

There are no substantial safety concerns that would require a REMS or RiskMAP. Other nasal corticosteroids also do not have REMS and RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Ciclesonide is not a new molecular entity. Nasal corticosteroids are a well-studied drug class, and efficacy and safety of this class of drug, including for another nasal formulation of ciclesonide, are

well understood. The efficacy and safety findings seen in the clinical program were obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

Sunovion has submitted a request for deferral of pediatric studies below 12 years of age and waiver of pediatric studies below 2 years of age. The lower age bound of 2 years 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 are 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. Sunovion's lower age cut off for the clinical program is appropriate. 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.

Sunovion plans to investigate the safety and efficacy of Zetonna Nasal Aerosol in 6 to 11 year olds and in 2 to 5 year olds sequentially, which is appropriate to assure safety in the younger age group. Because Zetonna Nasal Aerosol appears to be on a plateau of the dosing curve and has higher systemic absorption and higher local nasal retention than Omnaris Nasal Spray, lower doses of Zetonna Nasal Aerosol may need to be investigated in the pediatric program

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audits were requested for the two sites that reported nasal septal perfomration. DSI review of these sites did not demonstrate any findings that bring into question data integrity. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There were two investigators with significant equity interest in Sunovion or Nycomed or their predecessors. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC and other groups within the Agency.

12. Labeling

a. Proprietary Name

Sunovion initially submitted [redacted] (b) (4) as the proposed proprietary name. The DMEPA rejected this proposed name [redacted] (b) (4)

Sunovion subsequently submitted Zetonna as the proposed proprietary name, which was found to be acceptable by the DMEPA.

b. Physician Labeling

Sunovion submitted a label in the Physician Labeling Rule format that generally contains information consistent with other product label of this class. The label was reviewed by various disciplines of this Division, and by DDMAC. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DDMAC, and DMEPA, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, and DRISK, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Sunovion has submitted adequate data to support approval of Zetonna Nasal Aerosol (ciclesonide nasal aerosol) for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older at the proposed dose of 1 actuation per nostril once daily (37 mcg ex actuator per actuation). The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk and benefit assessment of Zetonna Nasal Aerosol supports its approval for relief of symptoms of SAR and PAR in patients 12 years of age and older without any specific restrictions. The safety findings of specific note were the two nasal septum perforations. Nasal septum perforation is a known safety signal for nasal corticosteroids, but is typically seen in post-marketing setting, and not common in NDA studies. The two perforations occurred in the short-term studies, and in the lowest Zetonna Nasal Aerosol dose treatment groups. Nasal ulcerations, which often precede development of nasal septum perforation were not higher with Zetonna Nasal Aerosol compared to placebo. But local nasal adverse reactions occurred more commonly with Zetonna Nasal Aerosol

compared to placebo, and also more patients on Zetonna Nasal Aerosol compared to placebo discontinued from studies for these local nasal adverse reactions. Currently marketed Omnaris Nasal Spray aqueous formulation also had local nasal adverse reactions, but there were no nasal septum perforations in the NDA studies. The seeming worse local nasal adverse reactions of Zetonna Nasal Aerosol are balanced by its robust efficacy findings. All doses of Zetonna Nasal Aerosol tested in various clinical studies showed efficacy, whereas in Omnaris Nasal Spray studies only the labeled dose was efficacious and doses half of the labeled dose or lower did not show efficacy (Section 14.1 of Omnaris Nasal Spray product label). Also Zetonna Nasal Aerosol showed improvement in RQLQ and TOSS (ocular symptom score) in SAR patients, which are not typically seen with nasal corticosteroids. The safety and efficacy differences between the two nasal ciclesonide products may be due to differences in delivery characteristics. Systemic exposure to active ciclesonide metabolite from Zetonna Nasal Aerosol is approximately 4 fold higher compared to Omnaris Nasal Spray (based on Cmax), and also local nasal delivery and retention from Zetonna Nasal Aerosol seems to be higher compared to Omnaris Nasal Spray (based on scintigraphy study). Another point of note in favor of Zetonna Nasal Aerosol is that all intranasal corticosteroids currently available in the US are aqueous-based formulations that are often associated with back-of-the-throat run off or post-nasal drip. In the past, there were CFC-based intranasal corticosteroid aerosol products, but these are not currently available because of phase-out of CFCs. Zetonna Nasal Aerosol will provide a non-CFC based intranasal corticosteroid aerosol treatment option that does not currently exist in the US.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Sunovian will conduct a required post-marketing safety study to further assess and define the frequency of local nasal adverse reactions for Zetonna Nasal Aerosol. A controlled clinical safety study is necessary because spontaneous adverse event reporting or other surveillance mechanism will not be able to discriminate the difference of frequency for local nasal adverse reactions between Zetonna Nasal Aerosol and other nasal corticosteroids. The result of such a safety study will help inform health care providers to better balance possible efficacy advantage of Zetonna Nasal Aerosol to possible safety disadvantage while deciding to prescribe Zetonna Nasal Aerosol. This study will further assess ocular safety of Zetonna Nasal Aerosol, which was not systemically assessed in the submitted program. Although there were no spontaneous reported ocular safety signals for Zetonna Nasal Aerosol, the prior assumptions of safety are less relevant now given that the systemic exposure and local nasal delivery and retention from Zetonna Nasal Aerosol are now known to be higher compared to Omnaris Nasal Spray.

The scope of the study will be somewhat similar to the PAR study 633. The study will be at least 6 months in duration and will have at least 300 patients (completers) each in two treatments arms - Zetonna Nasal Aerosol and an active nasal corticosteroid (the currently marketed Omnaris Nasal Spray aqueous formulation). A 6-month study is adequate because local nasal adverse reaction including nasal septum perforations were seen in

short-term AR studies. The study will include all patients with allergic rhinitis who are candidates for nasal corticosteroids and will include a reasonable number of patients with coexisting nasal conditions such as other related nasal diseases and prior nasal surgeries.

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/s/

BADRUL A CHOWDHURY
01/20/2012