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RESEARCH**

APPLICATION NUMBER:
202129Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	202129
Brand Name:	TBD
Generic Name:	Ciclesonide
Indication:	Symptoms associated with seasonal and perennial allergic rhinitis in adults and children 12 years of age and older
Dosage Form:	Nasal aerosol
Strengths:	37 mcg ciclesonide/actuation
Route of Administration:	Intranasal
Dosing regimen:	One actuation per nostril once daily
Applicant:	Nycomed Pharmaceuticals Inc.
OCP Division:	DCP2
Clinical Division:	DPARP (OND-570)
Submission Date:	March 18, 2011
Reviewers:	Ying Fan, Ph.D
Team Leader:	Suresh Doddapaneni, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 202129 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics findings

Ciclesonide nasal aerosol is supplied as a metered dose aerosol canister with a nasal actuator specifically designed for intranasal use. Two Ciclesonide products are currently marketed by Nycomed, an inhalation aerosol in a solution containing HFA-134a and ethanol delivered via a metered-dose inhaler (MDI) for the treatment of asthma (marketed as ALVESCO[®]; ciclesonide MDI, NDA 21658), and a nasal spray in an aqueous suspension (AQ) delivered via a pump spray for the treatment of nasal symptoms associated with SAR and PAR (marketed as OMNARIS[®]; ciclesonide AQ, NDA 22004). In order to expand available intranasal corticosteroid treatment options for allergic rhinitis (AR), the ciclesonide MDI canister utilized for the ALVESCO product has been coupled with a new nasal actuator to allow for nasal administration of this existing formulation.

The Sponsor's drug development program is comprised of 10 studies in healthy subjects or patients with allergic rhinitis, including 2 pivotal Phase 3 SAR studies and one pivotal Phase 3 PAR study. The clinical pharmacology program includes relative BA study (Study M1-422), scintigraphy study (Study 060-101), PK/PD study (Study M1-601), HPA axis study (Study 060-610), and one *in vitro* drug-drug interaction potential study (Study 493/2007).

Relative Bioavailability

The relative bioavailability of ciclesonide nasal aerosol was conducted 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, 320 µg intranasal via HFA nasal aerosol, and ciclesonide 320 µg orally inhaled HFA metered dose inhaler (MDI). Results from this study demonstrated that HFA nasal aerosol has much lower systemic exposure than orally inhaled MDI, 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 the nasal aerosol relative to nasal spray.

Hypothalamic-pituitary-adrenal (HPA) Axis study results

The HPA axis suppression of ciclesonide nasal aerosol was conducted in Study 060-610. It is a Phase 3, 6-week, randomized, double-blind, placebo-controlled, parallel group, study in subjects 12 years and older with perennial allergic rhinitis. The results of this study demonstrated that ciclesonide (administered as 160 µg and 320 µg nasal aerosol or 200 µg nasal spray) does not significantly suppress serum cortisol levels.

Deposition of ciclesonide

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 ciclesonide via the nasal aerosol device 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 nasal spray, about 76% of the dose was deposited in the nasal cavity and about 23% was recovered in nasal wipes.

Drug-drug interaction (DDI) potential:

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

2 QUESTION BASED REVIEW

Ciclesonide nasal aerosol was formulated in three dose strengths for clinical investigation: (b) (4)

Actuation of these 3 product strengths delivers doses ex-valve of 50 mcg, 100 mcg and 200 mcg of ciclesonide per actuation. Ex-actuator, this corresponds to 37 mcg, 74 mcg, and 141 mcg, respectively, and these are reflected in the proposed labeling. Note that in the clinical development program, terminology associated with the estimated delivery was utilized. The clinical studies primarily reference ex-actuator estimations of 40 mcg, 80 mcg and 160 mcg of ciclesonide per actuation (administered as once daily doses of 80 mcg, 160 mcg, and 320 mcg). These differences are in terminology only.

2.1 General Attributes/Background

2.1.1 What is the pertinent regulatory background of ciclesonide?

There are two ciclesonide products approved by Agency: ALVESCO[®] ciclesonide MDI (NDA 21658) and OMNARIS[®] ciclesonide AQ (NDA 22004). They are both sponsored by Nycomed. Alvesco ciclesonide MDI is an inhalation aerosol in a solution containing HFA-134a and ethanol delivered via a metered-dose inhaler (MDI) for the treatment of asthma. Omnaris ciclesonide AQ is a nasal spray in an aqueous suspension (AQ) delivered via a pump spray for the treatment of nasal symptoms associated with SAR and PAR.

The Ciclesonide nasal aerosol used the ciclesonide MDI canister for the ALVESCO product coupled with a new nasal actuator to allow for nasal administration of this existing formulation. It expands available intranasal corticosteroid treatment options for allergic rhinitis (AR).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

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 precise mechanism of how ciclesonide affects allergic rhinitis symptoms is not known.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of ciclesonide nasal aerosol is 1 actuation per nostril once daily (37 mcg/actuation). The maximum total daily dosage should not exceed 1 actuation in each nostril (74 mcg/day). The proposed route of administration is by the intranasal route only.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies and clinical studies used to support dosing or claims?

The summary of the clinical pharmacology studies are listed in the following table (Table 1). The clinical pharmacology program includes relative BA study (Study M1-422), scintigraphy study (Study 060-101), PK/PD study (Study M1-601), HPA axis study (Study 060-610), and one *in vitro* drug-drug interaction potential study (Study 493/2007).

Table 1. Summary of the clinical pharmacology studies

Study #	N	Design	Dose	Duration	Notes
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) Low systemic exposure compare to MDI inhalation Label claim
060-101	10 healthy (18-65 yrs)	OL, fixed treatment sequence	160 nasal aerosol 200 nasal spray	SD	Scintigraphy study (b) (4)
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 Too short to see the PD effect
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 No PK Label claim
493/2007	Inhibition on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 (in vitro)				DDI potential Label claim

* DX: dexamethasone, 6 mg QD 4 days

Because ciclesonide nasal aerosol is local acting, the dose selection is mainly based on the efficacy endpoints instead of systemic exposure of the drug. The dose selection of ciclesonide nasal aerosol was based on the Phase 2 dose-ranging study, M1-602, which included 80 mcg, 160 mcg, 320 mcg, and placebo, all administered once daily. This study formed the basis of dose selection to optimize efficacy relative to safety for further evaluation in Phase 3 studies (Study 060-622, Study 060-633, Study 060-634), which included the 80 mcg and 160 mcg doses. In the pivotal Phase 3 studies, both doses were effective in improving subject-assessed reflective and instantaneous total nasal symptom scores (ie, TNSS) with the 160 mcg dose not demonstrating sufficiently meaningful incremental benefit over the 80 mcg dose. The summary of the clinical studies are listed below in Table 2. For final assessment of the clinical efficacy and safety findings from these studies, please see Dr. Robert Lim’s Clinical review.

Table 2. Summary of the clinical studies

Study #	N	Design	Dose	Duration	Notes
FHP-017	24 SAR (18-45 yrs)	R, DB, PC, 2-way cross over	400 mcg QD Placebo	7 days	Pilot study Efficacy, safety
M1-602	513 SAR (≥12 yrs)	MC, R, DB, PC, PG, dose range	80 mcg QD 160 mcg QD 320 mcg QD Placebo QD	2 wks	Safety Optimal dose QD
060-622	707 SAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	2 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, rTOSS, iTOSS RQLQ(S)
060-633	1111 PAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	26 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, RQLQ(S)
060-634	671 SAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	2 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, rTOSS, iTOSS RQLQ(S)
060-635	~800 PAR (≥12 yrs)	MC, OL, SG	160 mcg QD	26 wks	Long term safety

R: Randomized; DB: double blinded; MC: multiple centers; PC: placebo controlled; SG: single group; PG: parallel group; DX: dexamethasone, 6 mg QD 4 days; iTNSS: instantaneous total nasal symptom score; rTNSS: reflective total nasal symptom score; iTOSS: instantaneous total ocular symptom score; rTOSS: reflective total ocular symptom score; RQLQ(S): rhinoconjunctivitis quality of life questionnaire with standardized activities

2.2.2 What is previously known about the pharmacokinetics of ciclesonide?

The following is the PK information from approved Omnaris ciclesonide nasal spray and Alvesco ciclesonide inhalation aerosol:

Absorption:

Ciclesonide and des-ciclesonide have negligible oral bioavailability (both less than 1%) due to low gastrointestinal absorption and high first-pass metabolism. The intranasal administration of ciclesonide at recommended doses results in negligible serum concentrations of ciclesonide (LLOQ 25 pg/mL). However, the known active metabolite (des-ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide (LLOQ 10 pg/mL). In a crossover study in 29 healthy adults, the median C_{max} was less than 10 pg/mL and 602 pg/mL following a single dose of ciclesonide nasal spray (300 mcg) and orally inhaled ciclesonide (Alvesco 320 mcg), respectively.

Distribution:

Following intravenous administration of 800 mcg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide was approximately 2.9 L/kg and 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged $\geq 99\%$ each, with $\leq 1\%$ of unbound drug detected in the systemic circulation.

Metabolism:

Ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by esterases. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP 2D6.

Elimination:

Following intravenous administration of 800 mcg of ciclesonide, the clearances of ciclesonide and des-ciclesonide were high (approximately 152 L/h and 228 L/h, respectively). The mean half life of ciclesonide and des-ciclesonide was 0.71 hours and 6 to 7 hours respectively. ¹⁴C-labeled ciclesonide was predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination.

2.2.3 What is the new pharmacokinetic information gathered for ciclesonide from current program?

The pharmacokinetic (PK) of ciclesonide nasal aerosol was evaluated in relative bioavailability study (Study M1-422), and PK/PD safety, tolerability study (Study M1-601).

Single dose PK:

Relative bioavailability study (Study M1-422) is a randomized, open-label, single-dose, 3-period, crossover study. Healthy subjects (n=29) received 3 single-dose sequential treatments of ciclesonide 300 µg intranasal via aqueous nasal spray, 320 µg intranasal via HFA nasal aerosol, and ciclesonide 320 µg orally inhaled HFA metered dose inhaler (MDI). Results from this study demonstrated that HFA nasal aerosol has much lower systemic exposure than orally inhaled MDI, approximately 10% of maximum exposure (C_{max}) and 15% of overall exposure (AUC_{inf}).

The mean serum concentration-time profile of Des-CIC (active metabolite) and ciclesonide following administration of the nasal aerosol formulation is shown in comparison to the oral inhalation and aqueous nasal dosage forms (Figure 1). Ciclesonide concentrations were undetectable following intranasal administration of ciclesonide aqueous nasal spray. The serum concentrations of ciclesonide were detectable in most samples following oral inhalation of ciclesonide up to 4 hours and following intranasal administration up to 2 hours (ciclesonide nasal aerosol). The mean C_{max} of ciclesonide and des-CIC following oral inhalation of ciclesonide were clearly higher compared to the nasal route of administration.

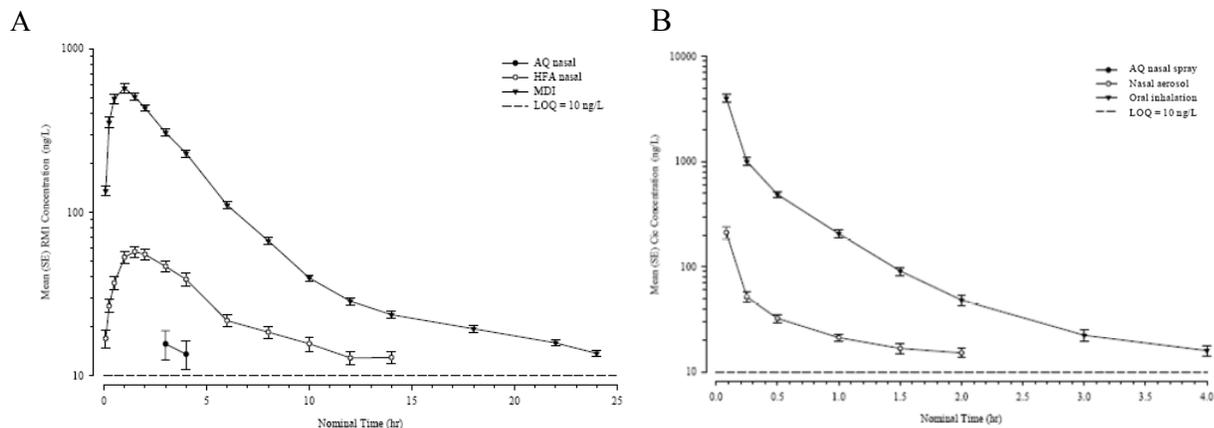


Figure 1 Mean Serum Concentrations of Des-CIC (A) and ciclesonide (B) Following a Single Intranasal Dose Aqueous Nasal Spray or Ciclesonide Nasal Aerosol or a Single Orally Inhaled Dose of Ciclesonide

Table 3. Primary Pharmacokinetic Parameter Estimates (mean) for the Metabolite Des-CIC and ciclesonide in Serum of Healthy Subjects in All Treatments:

	Ciclesonide nasal spray		Ciclesonide nasal aerosol		Ciclesonide oral inhalation	
	Cmax (pg/mL)	AUC _{0-∞} (ng•hr/L)	Cmax (pg/mL)	AUC _{0-∞} (ng•hr/L)	Cmax (pg/mL)	AUC _{0-∞} (ng•hr/L)
Des-CIC	15.20	NC	59.09	397.5	586.2	2685
Ciclesonide	NC	NC	225.8	103.6	3996	1136

As shown in Table 3, the mean Cmax and AUC_{0-∞} of Des-CIC and ciclesonide were substantially lower in the nasal aerosol group when compared to the ciclesonide oral inhalation group. The mean Cmax of Des-CIC was 59.1 pg/mL following a single dose of ciclesonide nasal aerosol (320 mcg) compared to 586.2 pg/mL following a single dose of orally inhaled ciclesonide (320 mcg). The mean Cmax of ciclesonide was 225.8 pg/mL following a single dose of ciclesonide nasal aerosol (320 mcg) compared to 3996 pg/mL following a single dose of orally inhaled ciclesonide (320 mcg). Between nasal spray and nasal aerosol products, the mean Cmax of Des-CIC was about four higher with the nasal aerosol relative to nasal spray.

Multiple- dose PK:

The multiple-dose PK of ciclesonide was evaluated in Study M1-601. Study M1-601 was a randomized, placebo-controlled, double-blind, 3-period crossover study. It examined the safety, tolerability, pharmacokinetic, and pharmacodynamic characteristics of ciclesonide HFA nasal aerosol 160 µg and 320 µg /day given as a nasal aerosol for 14 days to 18 healthy and 17 asymptomatic subjects with PAR. It also evaluated the PK profile of ciclesonide and the metabolite-Des-CIC.

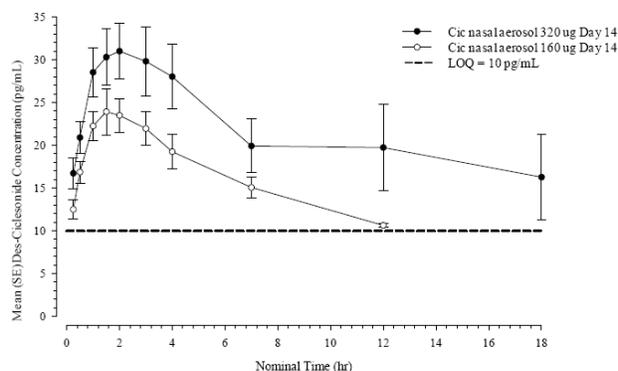


Figure 2. Mean (\pm SE) Serum Concentration of Des-CIC on Day 14 following repeated doses of ciclesonide nasal aerosol in the combined group

As shown in Figure 2, the mean serum concentration-time profile of des-CIC following 320 mcg ciclesonide nasal aerosol was higher compared to the lower dose (160 mcg via nasal aerosol). The pharmacokinetic parameter estimates of Des-CIC on Day 1 and Day 14 are provided in Table 4 for the ciclesonide 160 mcg and 320 mcg treatment groups. The mean C_{max} values of the higher dose of 320 mcg were 35.3 pg/mL on Day 1 and 35.84 pg/mL on Day 14 while the 160 mcg dose level values were 32.05 pg/mL and 25.98 pg/mL for the same respective days (Table 4).

Table 4. Pharmacokinetic Parameter Estimates of the Metabolite Des-CIC of Ciclesonide Nasal Aerosol on Day 1 and Day 14 in Serum in All Treatments

Ciclesonide 320 mcg				Ciclesonide 160 mcg			
Day 1		Day 14		Day 1		Day 14	
C _{max} (pg/mL)	AUC _t (pg•hr/mL)						
35.3	166.5	35.84	213	32.05	142.7	25.98	112.3

AUC_t: area under the concentration-time curve from time zero to the last quantifiable drug concentration

Overall, the data does not indicate significant drug accumulation over the treatment period.

The comparison of the PK in healthy and PAR patients:

In Study M1-601, the PK comparison of ciclesonide in healthy and PAR patients was also evaluated. A summary of pharmacokinetic parameter for Des-CIC on Day 14 in healthy subjects and PAR patients is presented in Table 5. Overall, mean C_{max} and mean AUC_t values within each dosage level were generally similar between the healthy subjects and PAR patients.

Table 5: Pharmacokinetic Parameter Estimates of the Metabolite Des-CIC of Ciclesonide Nasal Aerosol on Day 14 in Healthy Subjects and PAR Patients

Ciclesonide 320 mcg Day 14				Ciclesonide 160 mcg Day 14			
Healthy (n=16)		PAR (n=18)		Healthy (n=15)		PAR (n=17)	
C _{max} (SE) (pg/mL)	AUC _t (SE) (pg•hr/mL)						
35.43 (4.097)	225.9 (53.94)	34.39 (4.65)	193.1 (43.38)	25.95 (2.26)	113.0 (15.49)	27.28 (3.95)	131.8 (27.63)

2.2.4 What is the impact of chronic ciclesonide nasal aerosol dosing on cortisol suppression?

Cortisol suppression data following chronic administration of ciclesonide nasal aerosol was obtained from different studies: PK/PD study (Study M1-601), and HPA axis study (Study 060-610). Pilot study (FHP-017) (on day 7 of each period take blood sample to determine the cortisol level in serum, no data submitted).

Study 060-610 is a Phase 3, 6-week, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study 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. Secondary objectives were to evaluate safety, tolerability, and efficacy (efficacy was assessed as a supportive measure of treatment compliance) across doses and modes of administration. Two doses of ciclesonide HFA nasal aerosol (160 and 320 mcg) and marketed dose of ciclesonide nasal spray (200 mcg) were used. 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 2 (Visit 3B) to Visit 9B after 6 weeks of treatment. There were no drug concentration measurements in this study. The compliance for the treatment periods 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.

As shown in Table 6, The LS mean difference in serum cortisol AUC (0-24) change from baseline was - 2.4 $\mu\text{g}\cdot\text{h}/\text{dL}$ (95% CI: -15.1, 10.2) for ciclesonide HFA 160 μg vs placebo HFA + placebo dexamethasone, and was -0.5 $\mu\text{g}\cdot\text{h}/\text{dL}$ (95% CI: -13.9, 13.0) for ciclesonide HFA 320 μg vs placebo HFA + placebo dexamethasone. It demonstrated that ciclesonide (administered as 160 μg and 320 μg nasal aerosol) did not suppress serum cortisol levels. A significant suppression in serum cortisol levels was demonstrated in the dexamethasone control group compared to placebo.

Table 6: 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 160 mcg (n=60)	Ciclesonide HFA 320 mcg (n=50)
Baseline Mean (SD)	167.7 (36.3)	173.1 (53.5)	171.7 (40.1)	183.2 (61.9)
End of treatment (Change from Baseline) Mean (SD)	-154.4 (40)	-2.7 (41.1)	-1.5 (34.1)	-7.7 (33.7)
LS Mean (SE) Diff Pbo LSM (95% CI)		-5.0 (4.6)	-2.6 (4.6) -2.4 (-15.1, 10.2)	-4.6 (5.0) -0.5 (-13.9, 13.0)

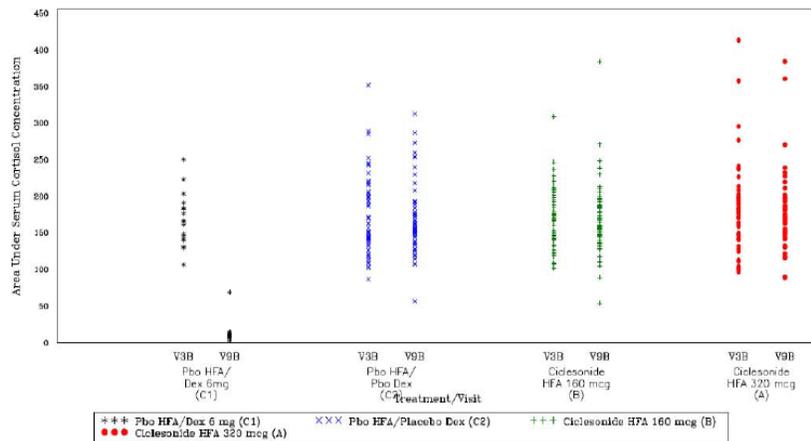


Figure 3: Vertical Scatter plot: Serum Cortisol AUC(0-24) (µg•h/dL) – HFA Treatment Groups

It should be noted that Study 060-610 was also designed to fulfill post marketing study 2 (to evaluate effects of ciclesonide nasal spray on the HPA axis) for the nasal spray product and was submitted to NDA 22004 (SDN 115; submission date April 11, 2011). This study was reviewed in detail under that submission.

The effect of ciclesonide on the HPA axis function is also evaluated in Study M1-601. As stated in Section 2.2.3, it is a 14 days study in both healthy and PAR subjects. Besides evaluating the PK of ciclesonide, it also evaluated the effect of ciclesonide on serum cortisol levels. However, from the pharmacodynamic standpoint, 14 days are not long enough to observe the HPA suppression. As such, Study 060-610 provided the primary data regarding the effect on HPA axis.

2.2.5 What is the deposition of ciclesonide with nasal aerosol?

The deposition of ciclesonide with nasal aerosol was investigated 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. Each subject was assigned to a fixed treatment sequence consisting of Regimen A: 160 mcg ciclesonide dose administered as a nasal aerosol from a novel HFA MDI device using the technique used in the Phase 3 trials (1 actuation per nostril; 80 mcg per actuation; ≤5 MBq ^{99m}Tc per 2 actuations); and Regimen B: 200 mcg ciclesonide administered as an AQ suspension from Omnaris® AQ nasal spray device according to the patient instruction leaflet (2 actuations per nostril; 50 mcg per actuation; ≤5 MBq ^{99m}Tc per 4 actuations). The range was 3 to 5 MBq for ^{99m}Tc.

Summary statistics for the initial ^{99m}Tc deposition data obtained for the ciclesonide nasal aerosol device are presented in Table 7. Nasal inhalation of ciclesonide via the nasal aerosol device resulted in deposition of almost the entire delivered dose in the nasal cavity (mean value of 98.36%) with very little variability 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).

Table 7: Summary Statistics for Initial Deposition Pattern as a Percentage of Delivered Dose: Ciclesonide Nasal Aerosol vs. Omnaris® Aqueous Nasal Spray

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

The results for the regional distribution in the nasal cavity as a percentage of the nasally delivered dose indicated that the formulation delivered from the Omnaris® AQ nasal spray device was evenly spread over the outer and middle regions (mean values of 52.41% and 42.43%, respectively). The spread from the ciclesonide nasal aerosol device was mainly located in the outer region (mean value of 78.28%) with a reduced amount in the middle region (mean value of 21.05%). Neither of the devices delivered the dose to the posterior region of the nasal cavity.

2.2.6 What is the proposed pediatric plan for ciclesonide nasal aerosol?

In a telecon dated September 28, 2011, the Agency recommended the sponsor to conduct dose ranging trials in the 6-11 yrs old population as lower doses may be effective in light of the scintigraphy data showing complete deposition of the dose in the nasal cavity with this product compared to nasal spray and use the lowest effective dose in the 2-5 yrs old population. In addition, the Agency indicated that the sample size of the sponsor proposed studies is insufficient to provide the evidence of local safety and recommended the sponsor to involve a larger safety population. For the sponsor’s proposed HPA axis study, the Agency recommended the sponsor to include the positive control arm.

The pediatric plan is undergoing finalization at the time of writing this review. The sponsor requested a waiver for children age 0 to less than 2 years of age and deferral of the pediatric study in ages 2 to 11 years. Sponsor proposes to evaluate the safety and efficacy of ciclesonide nasal aerosol in older children (6 to 11 years of age) prior to initiating studies in younger children (2 to 5 years of age). If efficacy and safety are demonstrated, these studies would be intended to support an indication for allergic rhinitis in this age group. The proposed studies in support of an allergic rhinitis indication in children 6 to 11 years of age and to fulfill the PREA requirements are: 6 week double blind (DB) HPA axis study in subjects with PAR at 74 mcg dose (Study 060-308), 2 week DB placebo controlled study in patients with SAR (b) (4) (Study 060-305), 12 week DB placebo controlled study in patients PAR (b) (4) (Study 060-306). The dose for children age 2 to 5 years will be determined based on the lowest effective dose from the studies in children 6 to 11 years of age. The proposed studies for children age 2 to 5 yrs include: 2 week DB SAR study, 12 week DB PAR study, and 6 week DB HPA axis study in subjects with PAR. This plan was discussed in PeRC meeting on November 30, 2011 and the committee agreed with the broader waiver and deferral plans. In the dose ranging trials in the 6 to 11 years age group, sponsor will be recommended to also include a lower dose (b) (4).

2.3 Extrinsic Factors

Is there any drug-drug interaction potential of ciclesonide with human CYP450 enzymes?

To evaluate ciclesonide as a direct inhibitor of CYP activity, human recombinant CYP (rCYP) enzymes were incubated with marker substrates in the presence or absence of ciclesonide (Study No. 493/2007). The target concentrations of ciclesonide ranged from 0.01 to 10 μM . In addition, ciclesonide was evaluated for its ability to function as a time-dependent inhibitor at the same concentrations as mentioned above, in which case ciclesonide was pre-incubated with human rCYP enzymes and an NADPH-generating system for 30 minutes to allow for the generation of metabolites that might inhibit CYP activity.

Under the experimental conditions examined, a 3 μM concentration of ciclesonide caused 55% inhibition of the rCYP2D6 activity ($\text{IC}_{50}=2.4 \mu\text{M}$), and 50% and 76% inhibition of the rCYP3A4 activity, as measured by testosterone 6 β -hydroxylation ($\text{IC}_{50}=2.4 \mu\text{M}$) and midazolam 1'-hydroxylation ($\text{IC}_{50}=0.734 \mu\text{M}$), respectively.

There was also evidence of direct inhibition of human rCYP2C9 and rCYP2C19. These enzymes were inhibited by 48% and 26%, respectively, in the presence of 3 μM ciclesonide; however, IC_{50} values for CYP2C9 and CYP2C19 could not be determined since less than 50% inhibition was observed at the highest concentration of ciclesonide that caused concentration-dependent inhibition (3 μM). There was little or no evidence of direct inhibition of human rCYP1A2, rCYP2A6, rCYP2B6, rCYP2C8, and rCYP2E1.

Considering that ciclesonide C_{max} following a single high dose in asthmatic patients is around 6 nM, clinical CYP interactions are unlikely.

2.4 General Biopharmaceutics

What is the relative bioavailability between the proposed product and the approved drug products?

Study M1-422 compared the systemic exposure of primary active metabolite, Des-CIC, in Omnisar (ciclesonide) Nasal Spray, Ciclesonide HFA Nasal Aerosol, and Orally Inhaled Ciclesonide in 30 healthy subjects. Results from this study demonstrated that ciclesonide HFA nasal aerosol has much lower systemic exposure than orally inhaled MDI. Specifically, the systemic exposure of Des-CIC in the ciclesonide nasal aerosol was approximately 10.1% of the mean C_{max} and 14.8% of the mean $\text{AUC}_{0-\infty}$ for the oral inhalation formulation. The systemic exposure of Des-CIC ciclesonide aqueous nasal spray was 2.6% for the mean C_{max} compared to the oral inhalation formulation. These findings suggest a much greater fraction of a ciclesonide dose is absorbed after oral inhalation compared to either nasal spray or nasal aerosol administration.

2.5 Analytical Section

What bioanalytical methods are used to assess concentrations?

One report (Study Report No. 243/2005) describes the validation study of the quantitative bioanalytical procedures used for the determination of ciclesonide and des-CIC in support of Study M1-422 and M1-601 provided in this NDA. Another bioanalytical method validation report (Study Report No. 92/2005) provides some additional stability information. In these validation studies, the general method consisted of extraction (solid phase or liquid-liquid), followed by liquid chromatography with tandem mass spectrometric detections. In addition, one report describes the validation study of bioanalytical procedures used for the determination of serum cortisol used in support of Study M1-601. All methods were validated with respect to sensitivity, accuracy, and precision.

Table 8 Summary of bio-analytical method and validation report

Bioanalytical method validation report No.	Bioanalytical Method			
	Method Brief	Method Specification and validation data		
243/2005	Automated liquid/liquid phase extraction followed by HPLC-MS/MS, sample volume 0.3 mL	Analyte	Curve Range (pg/mL)	%CV*
		Ciclesonide	10-2000	≤ 4.5 (LLOQ 15.3)
		Des-CIC	10-2000	≤ 8.3 (LLOQ 9.8)
92/2005	Automated liquid/liquid phase extraction followed by HPLC-MS/MS, sample volume 0.3 mL	Analyte	Curve Range (pg/mL)	%CV
		Ciclesonide	10-2000	≤ 12.7 (LLOQ 10.5)
		Des-CIC	10-2000	≤ 6.4 (LLOQ 16.4)
61/2008	Manual solid phase extraction followed by HPLC-MS/MS Sample volume: 0.25 mL	Analyte	Curve Range (pg/mL)	%CV
		Cortisol	1-250	NA

HPLC-MS/MS = high performance liquid chromatography with tandem mass spectrometry

%CV = coefficient of variation expressed as a percentage

*Acceptance criteria were met for all QC levels (≤ 20% at lowest level)

For Study 060-610, serum cortisol samples were analyzed [REDACTED] ^{(b) (4)} with an immunoassay using direct chemiluminescent technology for serum cortisol measurement (ADVIA Centaur XP system, Siemens). Because this assay is a commercially available, vendor-validated assay, the sponsor did not perform a full method validation.

Stability of ciclesonide and its metabolite (Des-CIC) in serum was demonstrated through 3 freeze/thaw cycles at -20°C, up to 4 hours at room temperature. Stability of cortisol serum was demonstrated through 4 cycles at -20°C, up to 4 hours at room temperature. Long-term storage stability of ciclesonide and its metabolite (Des-CIC) in serum at -20 °C was established up to 18 months and cortisol in serum at -20 °C was established up to 99 days.

3 PRELIMINARY LABELING RECOMMENDATIONS

Here are some high-level labeling comments. Line-by-line label edits will be done at a later date.

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The *blue bolded italic* words indicate the addition text, and the ~~bold strike through~~ words indicate the deletion.

12.3 Pharmacokinetics

Distribution: Following intravenous administration of 800 mcg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L per kg and 12.1 L per kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged $\geq 99\%$ each, with $\leq 1\%$ of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

(b) (4)

Drug-drug interactions: Ciclesonide inhibited human recombinant cytochrome P450 enzymes at high concentrations (*3 μM*) *in vitro*, but clinically relevant metabolic interactions are not anticipated. Based on *in vitro* studies in human liver microsomes, ciclesonide and des-ciclesonide appear to have no inhibitory or induction potential on the metabolism of other drugs metabolized by cytochrome P450 enzymes. *In vitro* studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a strong inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of the active metabolite of ciclesonide, des-ciclesonide, by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged.

In another drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, a moderate inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either des-ciclesonide or erythromycin.

4 APPENDIX

OCP Filing form

Office of Clinical Pharmacology New Drug Application Filing and Review Form <u>General Information About the Submission</u>				
Information		Information		
NDA/BLA Number	202129	Brand Name	To be determined	
OCP Division (I, II, III, IV, V)	II	Generic Name	Ciclesonide	
Medical Division	DPARP	Drug Class	Corticosteroid	
OCP Reviewer	Ying Fan	Indication(s)	Symptoms associated with seasonal and perennial allergic rhinitis ≥ 12 yrs	
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Nasal Aerosol	
Pharmacometrics Reviewer	N/A	Dosing Regimen	1 actuation/nostril QD (74 mcg/day)	
Date of Submission	03/18/2011	Route of Administration	Intranasal	
Estimated Due Date of OCP Review	11/16/2011	Sponsor	Nycomed Pharmaceuticals Inc.	
Medical Division Due Date	12/16/2011	Priority Classification	Standard	
PDUFA Due Date	1/20/2012			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	3		Study 243/2005 Study 92/2005 Study 61/2008
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Study M1-422
multiple dose:	x	1		Study M1-601
Patients-				
single dose:				
multiple dose:	x	1		Study M1-601
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x	1		Study 493-2007
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	1		Study 060-610 HPA axis
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	1		Study M1-601
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		Study M1-422
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1		
Literature References				
Others	x	1		Study 060-101 Scintigraphy
Total Number of Studies		9		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING FAN
12/16/2011

SURESH DODDAPANENI
12/16/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202129	Brand Name	To be determined
OCP Division (I, II, III, IV, V)	II	Generic Name	Ciclesonide
Medical Division	DPARP	Drug Class	Corticosteroid
OCP Reviewer	Ying Fan	Indication(s)	Symptoms associated with seasonal and perennial allergic rhinitis ≥ 12 yrs
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Nasal Aerosol
Pharmacometrics Reviewer	N/A	Dosing Regimen	1 actuation/nostril QD (74 mcg/day)
Date of Submission	03/18/2011	Route of Administration	Intranasal
Estimated Due Date of OCP Review	11/16/2011	Sponsor	Nycomed Pharmaceuticals Inc.
Medical Division Due Date	12/16/2011	Priority Classification	Standard
PDUFA Due Date	1/20/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	3		Study 243/2005 Study 92/2005 Study 61/2008
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Study M1-422
multiple dose:	x	1		Study M1-601
Patients-				
single dose:				
multiple dose:	x	1		Study M1-601
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x	1		Study 493-2007

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Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	1		Study 060-610 HPA axis
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	1		Study M1-601
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		Study M1-422
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1		
Literature References				
Others	x	1		Study 060-101 Scintigraphy
Total Number of Studies		9		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			Dose range study
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Dose-response instead
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	Rely on data from approved NDAs
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See Attachment 1 for a brief summary of the Clinical Pharmacology program.

No review issues were identified. However, following information request should be sent to the sponsor:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study Report No. 61/2008 contained bioanalytical assay validation data of cortisol in human serum samples from study M1-601. However, a similar report for Study 060-610 could not be found in the NDA. Provide assay validation data of cortisol in human serum samples from Study 060-610. Also, provide the individual serum cortisol AUC analysis dataset. If this information is already submitted, identify the location.

Ying Fan	May 2, 2011
<hr/>	
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	May 2, 2011
<hr/>	
Team Leader/Supervisor	Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Attachment 1

Clinical Pharmacology Summary

Nycomed (Nycomed has authorized Sunovion Pharmaceuticals Inc. to act as US Agent for this NDA) has submitted this original New Drug Application 505b(1) for Ciclesonide Nasal Aerosol indicated for treatment of symptoms associated with seasonal (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older.

Two Ciclesonide products are currently marketed by Nycomed, an inhalation aerosol in a solution containing HFA-134a and ethanol delivered via a metered-dose inhaler (MDI) for the treatment of asthma (marketed as ALVESCO[®]; ciclesonide MDI, NDA 21658), and a nasal spray in an aqueous suspension (AQ) delivered via a pump spray for the treatment of nasal symptoms associated with SAR and PAR (marketed as OMNARIS[®]; ciclesonide AQ, NDA 22004). In order to expand available intranasal corticosteroid treatment options for allergic rhinitis (AR), the ciclesonide MDI canister utilized for the ALVESCO product has been coupled with a new nasal actuator to allow for nasal administration of this existing formulation.

Ciclesonide nasal aerosol was formulated in three dose strengths for clinical investigation: [REDACTED] (b) (4) [REDACTED]. Actuation of these 3 product strengths delivers doses ex-valve of 50 mcg, 100 mcg and 200 mcg of ciclesonide per actuation. Ex-actuator, this corresponds to 37 mcg, 74 mcg, and 141 mcg, respectively. In the clinical development program, terminology associated with the estimated delivery was utilized. The clinical studies primarily reference ex-actuator estimations of 40 mcg, 80 mcg and 160 mcg of ciclesonide per actuation.

In this submission, the clinical efficacy and safety program of ciclesonide nasal aerosol was investigated in 10 studies in healthy subjects or patients with allergic rhinitis, including 2 pivotal Phase 3 SAR studies and one pivotal Phase 3 PAR study (Table 1). The clinical pharmacology program includes relative BA study (Study M1-422), scintigraphy study (Study 060-101), PK/PD study (Study M1-601), HPA axis study (Study 060-610), and one *in vitro* drug-drug interaction potential study (Study 493/2007) (Table 1).

Following are high level conclusions:

1. Ciclesonide nasal spray and ciclesonide nasal aerosol have relatively low systemic BA compared to ciclesonide oral inhalation (Study M1-422). C_{max} and $AUC_{0-\infty}$ of des-CIC with nasal aerosol was 10.1 fold and 14.8 fold lower than with oral inhalation product.
2. Deposition of ciclesonide with nasal aerosol: nasal cavity 98.4% (primarily), lungs 1.4% (negligible), nasopharynx 0.2% (minimal), none in stomach (Study 060-101)
3. PK of metabolite des-CIC were similar in healthy and PAR patients (Study M1-601)
4. No alteration of HPA axis at 160 or 320 mcg/day dose (Study 060-610)
5. Ciclesonide inhibited human CYP450 enzymes (CYP2D6, CYP3A4, CYP2C9 and CYP2C19) at high systemic concentrations (3 μ M) *in vitro* (Study 493/2007). However, inhibition is unlikely at therapeutic concentrations.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1. Summary of clinical and clinical pharmacology database

Study #	N	Design	Dose	Duration	Notes
FHP-017	24 SAR (18-45 yrs)	R, DB, PC, 2-way cross over	400 mcg QD Placebo	7 days	Pilot study Efficacy, safety (HPA axis)
M1-602	513 SAR (≥12 yrs)	MC, R, DB, PC, PG, dose range	80 mcg QD 160 mcg QD 320 mcg QD Placebo QD	2 wks	Safety Optimal dose QD
060-622	707 SAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	2 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, rTOSS, iTTOSS RQLQ(S)
060-633	1111 PAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	26 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, RQLQ(S)
060-634	671 SAR (≥12 yrs)	MC, R, DB, PC, PG	80 mcg QD 160 mcg QD Placebo QD	2 wks	Safety, efficacy (Pivotal) iTNSS, rTNSS, rTOSS, iTTOSS RQLQ(S)
060-635	~800 PAR (≥12 yrs)	MC, OL, SG	160 mcg QD	26 wks	Long term safety
M1-422	30 healthy (18-60 yrs)	R, OL, 3-way cross over	320 nasal aerosol (higher than proposed dose) 320 MDI inhalation 300 AQ nasal spray (higher than approved dose)	SD	Relative BA study (PK) Low systemic exposure compare to MDI inhalation Validation method available (Study 243/2005) Label claim
060-101	10 healthy (18-65 yrs)	OL, fixed treatment sequence	160 nasal aerosol 200 nasal spray	SD	Scintigraphy study (b) (4)
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 Too short to see the PD effect Validation method available (Study 243/2005, 61/2008)
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 No PK Label claim Validation method for serum cortisol missing
493/2007	Inhibition on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 (<i>in vitro</i>)				DDI potential Label claim

R: Randomized; DB: double blinded; MC: multiple centers; PC: placebo controlled; SG: single group; PG: parallel group; DX: dexamethasone, 6 mg QD 4 days; iTNSS: instantaneous total nasal symptom score; rTNSS: reflective total nasal symptom score; iTTOSS: instantaneous total ocular symptom score; rTOSS: reflective total ocular symptom score; RQLQ(S): rhinoconjunctivitis quality of life questionnaire with standardized activities

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING FAN
05/04/2011

SURESH DODDAPANENI
05/05/2011