DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202129

NDA APPROVAL

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated March 18, 2011, received March 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetonna (ciclesonide) Nasal Aerosol.

We acknowledge receipt of your amendments dated March 19, April 11, and 13, June 23, July 8, 18, and 22, September 1, 8, 13, 28, and 30, October 5, 6, 13, and 21, November 8, and December 6, 9, 15, 19, and 30, 2011, and January 2, 3, 4, 6, 9, 11, 12, 18, and 19, 2012.

This new drug application provides for the use of Zetonna (ciclesonide) Nasal Aerosol for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on January 12, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202129**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Colette Jackson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3322
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Colette Jackson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3322
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages zero to less than 2 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. This is because there are concerns of local and systemic toxicity with corticosteroids, and other treatments are available for allergic rhinitis.

We are deferring submission of your pediatric studies for ages 2 through 11 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1864-1 Conduct a 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally the steady-state PK profile after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	June 2012
Final Report Submission:	December 2013

1864-2 Conduct a 2-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	December 2012
Final Report Submission:	December 2013

1864-3 Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	December 2012
Final Report Submission:	December 2013

1864-4 Conduct a 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2014
Trial Completion:	December 2015
Final Report Submission:	May 2016

1864-5 Conduct a 12-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. The primary efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2014
Trial Completion:	December 2015
Final Report Submission:	May 2016

1864-6 Conduct a 6-week double blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	May 2014
Trial Completion:	December 2015
Final Report Submission:	December 2016

Submit the protocols to your IND 74674, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED**

PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

This product is appropriately labeled for use in ages 12 to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of nasal and ocular adverse events with the class of corticosteroids, of which Zetonna (ciclesonide nasal aerosol) is a member.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of nasal and ocular adverse events

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1864-7	Conduct a randomized clinical trial in adolescent (age 12 years and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of ciclesonide nasal aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS (ciclesonide) Nasal Spray.

The timetable you submitted on January 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2012
Trial Completion:	June 2013
Final Report Submission:	December 2013

Submit the protocol to your IND 74674, with a cross-reference letter to this NDA. Submit the final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1864-8 Improve the product robustness by exploring options to decrease the incidence of separation of canister from actuator and decreasing observed overcounting of the dose counter upon drop testing from a height of 1 meter. Final report submission should include the redesign information and drop testing results with the redesigned drug product, and will be submitted as prescribed in the comparability protocol.

The timetable you submitted on January 18, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2013

Submit clinical protocols to your IND 74674 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

BADRUL A CHOWDHURY
01/20/2012