CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

APPROVAL LETTER

NDA 20-746

AstraZeneca
725 Chesterbrook Blvd
Wayne PA, 19087-5677

Attention: Eric Couture, Ph.D.
Director, Regulatory Liaison

Dear Dr. Couture:

Please refer to your new drug application (NDA) dated July 29, 1996, received July 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort Aqua (budesonide) Nasal Spray.

We acknowledge receipt of your submissions dated October 10, November 1, 4, 5, 8, 15, 20, 21, and 27, and December 3, 1996, January 20 and 22, February 19, March 6 and 12, April 17, May 9 and 22, June 3, 13, and 16, September 8, 16, and 30, and October 7 and 15, 1997, February 27, April 2, May 6 and 14, June 9 and 15, and December 23, 1998, April 28, May 6, 18, 24, 25, and 27, June 3 and 8, July 20 and 30, August 13 and 30, and September 24, 27, and 30, 1999. Your submission of July 20, 1999 constituted a complete response to our June 22, 1999 action letter.

This new drug application provides for the use of Rhinocort Aqua (budesonide) Nasal Spray for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, patient package insert, and immediate container and carton labels submitted September 24, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. As discussed with the Division in a teleconference on July 26, 1999, and as committed to in your September 27, 1999, submission, within three months of launch you will utilize the immediate carton and container labels identical to those submitted on September 27, 1999.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-746." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated August 30 and September 30, 1999. A summary of these commitments, along with any completion dates agreed upon, are listed below. Please note that the numbers and letters in the parentheses refer to the specific items from the August 30, 1999, submission.

1. You will evaluate data from twenty post-approval batches and will submit, nine months from the date of this letter, a prior-approval supplement with appropriate final specifications for drug product. (Comment 3, Item 3.a.)

2. You will work closely with your to improve the consistency of the dosage performance. You will submit within nine months from the date of this letter a final, data-based acceptance criteria for in a prior-approval supplement, as specified in Item 1 above. (Comment 3, Items 3.b., 3.g. and 3.a.)

3. You will work with your to tighten specifications for acceptance criteria for on components extracted with. You will evaluate data from the supplier as well as your own data generated during the 9-month post-approval period and submit final acceptance criteria for at the time of submission of the final drug product specifications. (Comment 3, Item 3.e. and Comment 2, Item3.a.)

4. You will evaluate data from twenty post-approval batches and submit a prior-approval supplement containing final method and acceptance criteria for the measurement of color of the drug product. You commit to submitting data for Index measurements for the suspension and continuing to investigate the feasibility of a method for the filtrate. You will investigate alternative sample preparation methods and will provide a report of your findings to the Division by December 31, 1999. If you determine a suitable method, you also commit to submitting measurements that are collected on the first 20 manufacturing batches. (Comment 3, Item 3.c.)

5. You will work with the manufacturer of the on monitoring the of their product.You will evaluate data from twenty post-approval batches in connection to the, and submit, nine months from the date of this letter, a prior-approval supplement with final method and acceptance criteria for the measurement of of the drug product. (Comment 3, Item 3.d.)

6. With regard to acceptance criteria for, you will investigate the possibility of harmonizing it with the drug product acceptance criteria for. You will evaluate the data from twenty post-approval batches and will submit, nine months from the date of this letter, a prior-approval supplement for final specification for. (Comment 3, Item 3.f.)

7. You will submit a prior-approval supplement establishing supplier, when adequate

8. You will provide the results from an *in vitro* test for and an *in vitro* test for stability data are available. (Comment 3, Item 3.i.)assay) of to the Agency by November 30, 1999. (Comment 3, Item 3.j.)

9. You will evaluate the data for 20 lots of drug substance and will propose, in a prior-approval supplement submitted nine months from the date of this letter, an appropriate final specification for budesonide. (Comment 2, Item 1.b.)

10. You will conduct a long-term, double-blind, placebo controlled growth study in children, and provide a completed study report by December 2002. You will revise your labeling based on the results of this study.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, we remind you of the following agreement specified in your submissions dated August 30, 1999 (Comment 3, Item 3.m.) and September 24, 1999. The first three full-scale production batches for each strength and pack size will be placed on stability under the accelerated, intermediate, and long-term (upright and inverted storage) stability protocols, as provided in your August 30, 1999, submission. For second, and subsequent years of

production, a minimum of one batch per year will be placed on stability for each pack size and strength of drug product. The algorithm for the number of batches randomly selected for stability testing is as follows:

- If 1-33 batches are produced in a year, then one full-scale batch will be tested;
- if 34-66 batches are produced in a year, then two full-scale batches will be tested;
- if 67-100 batches are produced in a year, then three full-scale batches will be tested; and
- if >100 batches are produced in a year, then four full-scale batches will be tested.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until June 30, 2001.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. The Division will continue to work with you on your request to amend the written request which issued December 14, 1998. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL