CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20233/S003

APPROVAL LETTER

FEB 7 1996

NDA 20-233/S-001 and S-003

Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

Attention: Larry M. Paglia, Ph.D.
Director, Regulatory Affairs

Dear Dr. Paglia:

Please refer to your July, 1, 1994 and August 17, 1995 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort (budesonide) Nasal Inhaler.

These supplemental applications provide for changes to the labeling as follows:

S-001 - a revision to the Patient's Instructions to correct a discrepancy between the Patient's Instructions and Dosage and Administration section. Specifically the statement therefore very important that Rhinocort is used was changed to "It is therefore very important that Rhinocort is used regularly" to reflect the once daily dosing alternative;

S-003 - a revision to the Patient's Instructions to ensure proper use of the inhaler.

We have completed the review of these supplemental applications including the submitted draft labeling and supplement S-003 is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 17, 1995.

Please submit fifteen 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 "FINAL PRINTED LABELING" for

approved supplemental NDA 20-233/S-003. Approval of the submission by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

Supplement S-001 has been superseded with the approval of supplement S-003, therefore, the information contained in S-001 will be retained in our files. 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, please contact:

Sandy Barnes
Project Manager
(301) 827-1075

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 14 1994

NDA 20-233

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
Princeton, New Jersey 08540

Attention: Gregory M. Hockel, Ph.D.
Senior Director
Regulatory Affairs

Dear Dr. Hockel:

Please refer to your December 20, 1991 new drug application and your resubmission dated December 30, 1992 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort (budesonide) Nasal Inhaler.

We also acknowledge receipt of nineteen amendments noted on the attached page.

This new drug application provides for the treatment of seasonal and perennial allergic rhinitis.

We have completed the review of this application including the draft labeling submitted on December 17, 1993 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 draft labeling. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the December 17, 1993 draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the final printed version of the revised FPL as soon as possible. This submission should be designated for administrative purposes as "FPL for approved NDA 20-233." Approval of this label is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

As a reflection of our mutual understanding of the importance of initial promotional campaigns on physicians' use of a new drug, we note your commitment to work with us and with the Division of Drug Advertising and Labeling on this advertising program to develop an introductory campaign satisfactory to all concerned. Please submit prior to implementing, one copy to this division and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Communication
HFD-240 Room 11B-06
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed material in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

While all other aspects of this application have been approved the required validation of the analytical methods has not been completed. In such cases, the policy of the Center for Drug Evaluation and Research is to proceed with approval. We expect your cooperation to help resolve expeditiously any problems that may occur with respect to validations.

We have also received your letter of February 9, 1994 agreeing to PHASE IV commitments which will include:

For your NEW IND formulation to be submitted in the first half of 1994, agree to:

1. Compare 400, 200, 100 and 50 mcg daily with placebo in both seasonal and perennial studies in adults and children. Budesonide may be very potent; is 50 mcg already at Emax?.

   Seasonal hayfever studies should be modeled like 2008 so that actual calendar day comparisons can be made and that

there is ample baseline and double-blind treatment and recovery times. 2008 had two weaknesses of design: no stratification or exclusion of patients whose symptoms were too mild and not enough differences between doses. These shortcomings should be avoided.

Dose ranging in perennial rhinitis should be amenable to a balanced Crossover design with adequate washouts and double-blind treatment periods.

2. Obtain placebo-controlled evidence of efficacy in "nonallergic" perennial rhinitis in children.

3. Using the highest marketed dose to look at growth, do a controlled, longterm repeated knemometry (plus predicted vs actual skeletal growth measurements) study in children with perennial rhinitis (terfenadine would be an acceptable control since one year would be too long for placebo).

4. Do an HPA study designed like 2147 including highest dose to be indicated.

5. Use of varied ethnic patients background for your safety and efficacy studies.

6. Due to the high degree of hepatic inactivation the sponsor needs to conduct a pharmacokinetic study in subjects with mild to moderate hepatic impairment as determined by elevation of enzymes, albumin concentrations, clinical assessments etc. (PUGH Score). At the present time the Agency is aware that the sponsor has conducted some type of hepatic study as part of the Pulmicort development program. Whether or not this study is sufficient at this time is unknown as the final study report has not been submitted for review. The sponsor needs to commit to submit the results of this study and should it be found to be inadequate to commit to perform another study with a mutually agreed upon protocol.

7. The pediatric study carried out as part of the Pulmicort investigations, and submitted in this NDA, is inadequate for assessing the bioavailability of this dosage form in the population. The technique of pooling the five initial samples and then taking the average concentration is not acceptable. Such a technique biases the AUC, Cmax, and Vd calculations. The study should be repeated to obtain adequate measures of the bioavailability of the dosage form in this population using a mutually agreed upon protocol as a phase IV commitment.

The protocols and other relevant details for satisfying the PHASE IV commitments should be cleared with the Division before initiation.

The original copy of the PHASE IV studies should be submitted to this Division, with a copy to the Division of Drug Information Resources, HFD-80. Since that Division is responsible for tracking PHASE IV studies, a copy of all future communications regarding PHASE IV studies should be sent to them.

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

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

Sincerely yours,

Pilot Drug Evaluation Staff Review Team
Center for Drug Evaluation and Research

Linda Katz, M.D.
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