CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

APPROVAL LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-929

AUG 8 2000

AstraZeneca LP
725 Chesterbrook Blvd
Wayne, PA 19087-5677

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

Dear Dr. Couture:

Please refer to your new drug application (NDA) dated November 18, 1997, received November 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Respules (budesonide inhalation suspension).

We acknowledge receipt of your submissions dated January 7, 15, and 30, February 5 and 6, March 5, 6, and 12, May 12, August 7 and 20, and November 30, 1998, April 9, and May 6, 1999, February 9, June 2 and 9, July 10 (2 submissions) and 25 (2 submissions), August 1, 3, 4, and 7, 2000. Your submission of February 9, 2000, constituted a complete response to our February 11, 1999, action letter.

This new drug application provides for the use of Pulmicort Respules (budesonide inhalation suspension) for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

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 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 submitted August 4, 2000, patient instructions for use, immediate container and carton labels submitted August 3, 2000). 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 committed to in your August 3, 2000, submission, within 4 months of launch (February 1, 2001) you will utilize only the immediate container and carton labels containing the revised statement "Do NOT use in an ultrasonic nebulizer."

Please submit 20 paper 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. Alternatively, you may submit the FPL electronically according to the guidance for

industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-929." 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 submission dated August 3, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. Study and report by October 1, 2003, the effects of maintenance therapy with Pulmicort Respules at recommended doses in the indicated population (≥1 year of age) on the immunogenicity of a live virus vaccine (e.g., varicella).

2. Continue on-going studies to further refine the [redacted] assays, and provide the data from these assessments along with resulting proposed specifications on or before October 12, 2000 (as committed to in attachment 4 of the August 3, 2000, submission).

3. Develop and validate an appropriate test method and propose a finished product specification for [redacted], by December 1, 2000.

4. Reevaluate and tighten the content uniformity specification based on data collected from post approval production batches by October 12, 2000, or at least 20 batches, whichever comes first.

5. Monitor for the [redacted] and establish final specifications based on data collected by December 31, 2000, or approximately 50 lots, whichever comes first.

Submit commitments 2 – 5 as individual prior approval supplements.

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 314.81(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."

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 July 31, 2002.

In addition, 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-42
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, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

APPROVABLE LETTERS

Trout

FEB 11 1999

NDA 20-929

Astra USA, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Attention: Michael C. Elia, Ph.D.
Director, Regulatory Liaison

Dear Dr. Elia:

Please refer to your new drug application (NDA) dated November 18, 1997, received November 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Respules (budesonide nebulizing suspension).

We acknowledge receipt of your submissions dated May 12, August 7 and 20, and November 30, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments. Please note that the references to comment numbers in parentheses refer to specific comments from our May 20, 1998, letter.

1. Include the test method for content uniformity in the specification sheet. (Comment 4.)

2. Regarding the specifications and test method for "Particle Size of Budesonide Micronized API and Budesonide Inhalation Suspensions by —— —— ' batch analysis data indicate that the proposed MMD is too wide and should be tightened to reflect actual data. (Comment 5.b.)

3. The following comments pertain to the —————— used in manufacturing the drug product. (Comment 8.)

   a. Provide information on the composition of the ———— used for manufacturing.

   b. Provide information on the ———————— and acceptance criteria for ———— used during manufacturing.

   c. Provide appropriate acceptance specifications for ———— The information should also be included in the manufacturing Standard Operating Procedures.

4. The composition, appropriate acceptance specifications, test methods and data for each of the packaging components [redacted] should be provided. (Comment 10.)

5. Regarding equivalency of secondary packaging from different sources, it is stated that samples of suspension from the primary stability batches which utilized [redacted] were tested for [redacted] However, the age of samples tested for [redacted] are not specified. Provide information on the batches which were tested for [redacted] impurities (e.g., age of the samples tested, actual data, and any trend of [redacted] level over time). [Comment 11.]

6. The following comments pertain to the [redacted] (Comment 12.)

   a. [redacted]

   b. [redacted]

7. It was reported that [redacted], and an "upright" storage position is recommended. However, the Respules may be stored in different orientations. To address this issue, a study of "horizontal" position along with "upright" position should be conducted. (Comment 15.)

8. The following comments pertain to the newly designed Pulmicort Respules.

   a. Make the word [redacted] more prominent.

   b. Explain [redacted]

9. We acknowledge receipt of your January 26, 1999, technical package regarding the adsorption of budesonide to the wall of the [redacted] container. This package was not reviewed prior to the issuance of the letter, and any deficiencies with regard to this issue which are not resolved by submission of the package will need to be discussed and adequately addressed prior to approval of this application.

10. We remind you of your commitment to reevaluate and tighten the content uniformity specification based on data collected from post approval production batches within 6 months from the date of approval, or at least 20

batches, whichever comes first. (Comment 4.)

In addition, it will be necessary for you to submit draft labeling according to the attached marked-up labeling, and including revisions based on the following comments.

11. The following comments refer to the **PHARMACODYNAMICS** section of the label.

    a. The statements "The effects of PULMICORT RESPULES on the hypothalamic-pituitary-adrenal (HPA) axis were studied in [redacted] For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with PULMICORT RESPULES treatment at recommended doses." do not accurately reflect the data. The data show a change from baseline in ACTH-stimulated cortisol levels and there was a statistically significant dose-dependent suppression of urinary free cortisol excretion. The statement in the labeling should be modified based on these relevant data.

    b. With regard to the following statement, '[redacted] the data suggest that patients on Pulmicort Respules did have more HPA-axis suppression than those on conventional therapy. Therefore, the above statement should be modified to accurately reflect the data.

12. The following comments are with regard to the **CLINICAL TRIALS** section.

    a. With regard to the following statement "Three double-blind, placebo-controlled, parallel [redacted] ' a significant decrease in nighttime and daytime asthma symptoms, or reduction in the need for bronchodilator therapy, was not observed in all studies with all dosing regimens. Furthermore, symptom reduction did not occur across race, and for Pulmicort Respules 1.0 mg once daily, a significant improvement in FEV_1 or morning PEF was only seen in 1 of 2 studies. Therefore, these statements should be modified to accurately reflect the data. [redacted]

b. In the **Patients Not Receiving Corticosteroid Therapy** subsection, the number of patients studied should be modified [redacted]. In addition, the graph in Figure 1 should be modified to [redacted]

c. In the **Patients Receiving Once Daily or Twice Daily Dosing** subsection, the number of patients studied should be modified to [redacted]. In addition, the graph in Figure 3 should be modified to [redacted]

13. The bolded paragraphs in the **WARNINGS** section should be placed in a black box.

14. In the **PRECAUTIONS:** [redacted] subsection, the statements "[redacted] should be modified to reflect the new class labeling for corticosteroids.

15. In the **DOSAGE AND ADMINISTRATION** section, following the instruction to administer PULMICORT RESPULES with a jet nebulizer, a statement warning against mixing PULMICORT RESPULES in the nebulizer with other medications should be added. This statement should also be included in the **Information for Patients** subsection and the *Patients Instructions for Use.*

Additional labeling comments may be forwarded following review of the requested data.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

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

ATTACHMENT

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-929
HFD-570/Div. Files
HFD-570/G.Trout /S/ 2-11-99
HFD-570/Chu
HFD-570/Meyer
HFD-570/Kim
HFD-570/Poochikian
HFD-870/Uppoor
HFD-570/Vogel
HFD-570/Sun
HFD-570/Elashoff
HFD-570/Wilson
HFD-002/ORM
HFD-102/ADRA
HFD-95/DDMS
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: GST/February 4, 1999
Initialed by: Schumaker/2-5-99
Kim/2-6-99
Poochikian/2-7-99 /S/ 2/11/99 /S/
Chu/2-5-99
Meyer/2-5-99
Vogel/2-5-99
Sun/2-5-99
Elashoff/2-8-99
M.L. Chen/2-9-99
Jenkins/2-10-99 & 2-11-1999
Final: Campbell/2-11-99
Filename: n:\staff\troutg\20929ae

R. Meyer reviewed + signed off via e-mail 2-11-99

2/11/99 /S/ 02/11/99

/S/ 2/11/99

APPROVABLE (AE)

14 Draft Labeling Page(s) Withheld

MAY 20 1998

NDA 20-929

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

Attention: Dennis Bucceri
Vice President,
Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your new drug application dated November 18, 1997, received November 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Respules (budesonide inhalation suspension).

We acknowledge receipt of your submissions dated January 7, 15, and 30, February 5 and 6, and March 6, 12, and 27, 1998. The user fee goal date for this application is May 20, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments.

The following comments pertain to the proposed drug product specifications and test methods.

1. The proposed specification for color (absorbance) is not justified; the specification should be significantly tightened to reflect the observed data. In addition, a relationship of the proposed absorbance units to a certain reference color standard should be established.

2. The method for " " should indicate the " " In addition, the proposed specification should be tightened to reflect actual data and there should be an upper limit; e.g., " "

3. The following comments pertain to the specification and test method for Edetate Disodium "

a. [redacted]

b. Provide information about the [redacted] observed levels) found in method [redacted]

c. State whether or not any other [redacted] were tested for [redacted]

d. The proposed specification does not reflect the stability data. The specification should be tightened to [redacted]

4. The content uniformity specification should be clearly spelled out and be reflective of the data for multiple batches. Moreover, the content uniformity test method should be described in detail, and an appropriate method number or procedure number should be assigned.

5. The following comments pertain to the specifications and test method for "Particle Size of Budesonide Micronized API and Budesonide Inhalation Suspensions by [redacted]

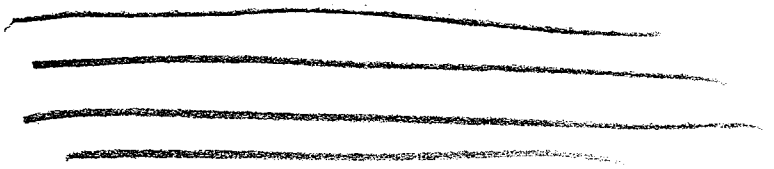
a. Provide reproducibility data and the reports [redacted] which were referenced in the validation studies. In addition, provide particle size distribution analysis printouts of different batches, including detailed operating parameters.

b. Batch analysis data indicate that the proposed specifications should be significantly tightened; e. g.,

[redacted]

6. The following comments pertain to the impurities and degradation products.

a. The specifications should be tightened to reflect the stability data as follows:



b. The LODs and LOQs for degradation products are too high. We strongly recommend that the analytical method be improved.

The following comments pertain to manufacturing.

7. Provide the correct name and address, including zip code, of the contract facility,

8. Provide information (composition and compatibility with the formulation components) on the used for manufacturing.

The following comments pertain to the container and closure system.

9. The application should include references to authorized drug master files (DMFs) for each of the packaging components (The information should include complete compositions, sources, acceptance/release criteria, test methods, data, etc.

10. The application should contain appropriate acceptance specifications, test methods, and data for each of the packaging components

Once the suppliers' test results are confirmed through multiple batches using appropriate test methods, shipments of packaging components may be accepted based on Certificates of Analysis (COAs) from the supplier. However, in the latter case, the results of COAs should be periodically validated on a pre-set schedule.

11. Equivalency of secondary packaging from different sources should be established, documented, and data submitted in terms of [redacted] into the respule.

12. The following comments pertain to the [redacted]

a. [redacted]

b. [redacted]

The following comments pertain to the drug product stability.

13. The stability protocol provided does not contain a specification and test method for " [redacted] This parameter should be a part of the stability protocol.

14. Acceptance criteria for stability should be the same as those for drug product specifications for shelf-life.

15. It is stated that [redacted] of storage; Pulmicort Respules are recommended to be stored "upright." Provide an explanation for the cause of the [redacted]

16. Provide information (nature, extent, etc.) about the [redacted] found in samples stored for [redacted] at 40°C/30% RH (Table 32, page 100, vol. 1.7) and define the impact of this finding at [redacted] Also provide the detection method for [redacted]

17. A [redacted] study [redacted] was reported. A study of subfreezing storage condition and its impact on the particle size distribution, [redacted] is recommended (see comment 16. above).

18. Appropriate data need to be submitted to qualify [redacted] used for [redacted] of [redacted] ampules. [redacted] on the [redacted] ampule is strongly recommended as an alternative to [redacted] Please also refer to comments 9. and 10. above.

19. The stability commitment and protocols should be updated; accelerated stability should be added to the protocol.

20. It is stated that deviations that do not affect the safety and efficacy of the product will be promptly discussed with the FDA's District Office according to 21 CFR 314.81(b)(1)(ii) in the post approval stability commitment (page 305, vol. 1.7). A statement "stability failures will also be discussed with the review division." should be added to the paragraph.

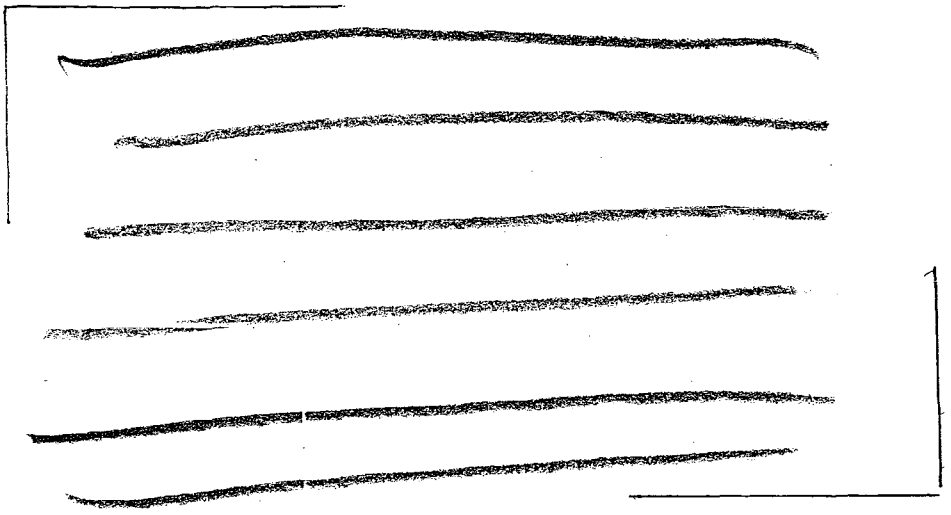
21. Provide updated stability data and protocol.

The following comment pertains to the Environment Assessment.

22. Regarding a request for categorical exclusion of environmental assessment, provide actual calculations which should include all the budesonide containing products for the estimated concentration of the drug substance at the point of entry into the aquatic environment.

The following comments pertain to the microbiology section of your submission.

23.



24.

25. Clarify whether the drug product suspension supports microbial growth.

The following comment pertains to the pre-clinical section of your submission.

26. The final report for the 3-month study in 1-2 week old dogs should be submitted.

It will be necessary for you to submit revised draft labeling incorporating the changes in the attached marked-up draft labeling and including the following revisions. Please note that these are preliminary labeling comments, and additional comments may follow once you have responded to the requests in this letter.

27. The established name should be revised to "budesonide inhalation suspension."

28. The tab portion of each unit should be extended/enlarged to allow [redacted]

29. [redacted]

30. In the PHARMACODYNAMICS section of the labeling, the sentence reading [redacted]" should be revised to more accurately reflect the data (i.e., based on the revised analyses submitted on March 27, 1998).

31. The following sentence in the CLINICAL TRIALS section of the labeling is inaccurate (i.e., the pre-specified primary and secondary endpoints were not consistently significantly greater from Pulmicort versus placebo across all studies and/or doses) and should be modified to accurately reflect the data: [redacted]

32. In the "Patients Previously Maintained on Inhaled Corticosteroids" subsection of the labeling, the following changes should be made.

    a. The sentence reading '[redacted]' should be deleted or modified to more accurately reflect the data.

    b. The sentence reading [redacted] should be modified to more accurately reflect the data (see also comment 38. below).

33. The following adverse events, that occurred with an incidence of 3% or more in at least one Pulmicort Respules group where the incidence was equal to or less than that of the placebo group, need to be included in a narrative listing following the Adverse Event table in the ADVERSE REACTIONS section of the label: sinusitis, pharyngitis, bronchospasm, bronchitis, [redacted]

34. Color mock-ups of the carton and container labels should be submitted

35. Submit the photographs which will be included in the Patient's Instructions for Use.

The following comments represent issues arising from the clinical review of this application that may significantly impact on product labeling.

36. [redacted]

37. [redacted]

38. [redacted]

If there are additional clinical data for the budesonide inhalation suspension (i.e., from recently completed studies or other sources) that have been developed subsequent to the submission which address these clinical issues (i.e., comments 36., 37., and 38), these data should be included in your response for our review. If additional clinical data are not available, provide a detailed analysis and rationale based on the existing data in support of the proposed claims.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials with this dosage form that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing the adverse reaction database at the time the NDA was submitted versus the time the NDA is resubmitted will facilitate review.

2. Retabulation of drop-outs in trials with this dosage form with new drop-outs identified. Discuss the circumstances of each dropout, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. WE will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(c) of the new drug regulations you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

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

ATTACHMENT

cc:
Original NDA 20-929
HFD-570/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-570/G.Trout
HFD-570/Chu
HFD-570/Meyer
HFD-570/Vogel
HFD-570/Sun
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Elashof
HFD-570/Wilson
HFD-870/Gillespie
HFD-870/Uppoor
HFD-102/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)

Drafted by: GST/May 11, 1998/n:\staff\troutg\20929.let

Initialed by: Vogel/5-18-98
Kim/5-18-98
Gillespie/5-18-98
Poochikian/5-19-98
Schumaker/5-19-98
Elashoff/5-19-98
Sun/5-19-98
Chu/5-19-98
Meyer-5-19-98
Jenkins/5-20-98

Final:

APPROVABLE (AE)

23 Draft Labeling Page(s) Withheld