CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-441/S002

CORRESPONDENCE

Memorandum of Telephone Facsimile Correspondence

Date: 10/01/98

To: Dennis Bucceri
Regulatory Affairs, Astra Pharmaceuticals

From: David Hilfiker
Project Manager

/S/

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: Labeling Recommendations

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

/S/ 10-1-98

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

cc: Original NDA 20-441/S-002
HFD-570/Div Files
HFD-570/Hilfiker
HFD-570/Schumaker
HFD-570/Purucker
HFD-570/Meyer

October 1, 1998

Dennis:

Attached is a marked-up version of your draft labeling with the revisions that we discussed earlier today. In addition to what was discussed, I noticed after our conversation that there were some revisions to incorporate into the PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection and the OVERDOSAGE section from a previous review. Please review those changes as in the enclosed marked-up label.

Please note that FDA additions are denoted by underlined text, and FDA deletions are denoted by strikeout.

If possible, please submit a revised draft label as an amendment to supplement 002 or let me know that you agree with the language proposed in the enclosed label. If you choose to submit an alternate label, please fax me a copy before sending it through the mail. My fax number is 301-827-1271.

Thank you for your prompt attention to this matter.

Dave Hilfiker
301-827-1046

15 **Page(s) Redacted**

Draft

Labeling

Memorandum of Telephone Facsimile Correspondence

Date: March 2, 1998

To: Dennis Bucceri
FAX # 508-836-8390

From: Gretchen Trout /S/
CSO, Division of Pulmonary Drug Products

Through: Mary Purucker, M.D. /S/
Medical Reviewer, Division of Pulmonary Drug Products

Subject: NDA 20-441/S-002

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Thank you.

APPEARS THIS WAY
ON ORIGINAL

Reference is made to your pending supplemental new drug application (NDA) for Pulmicort Turbuhaler. This supplement (S-002) provides for once daily dosing for Pulmicort Turbuhaler and was submitted on October 6, 1997. Pursuant to our review of pivotal clinical trial SD-004-0009, we request that Astra provide the following information/analyses.

1. The two primary endpoints, mean morning PEFR and FEV1, were reported separately for patients who were GCS-dependent and GCS-free prior to randomization (Vol. 1, p. 88).

2. Change from baseline in mean AM PEFR and FEV1, as well as p-values, for these primary endpoints for comparisons of each Pulmicort arm to placebo were reported separately for the GCS-dependent and GCS-free subgroups.

3. Time to treatment response based upon improvement in mean AM PEFR relative to baseline was calculated for each of the two Pulmicort Turbuhaler arms for the intent-to-treat LVCF across phases population. (Vol. 1, p. 91).

4. Patients who were managed on inhaled corticosteroids at baseline were switched to inhaled beclomethasone dipropionate (BDP) during the two-week baseline period. We have not been able to locate a description of the rules used to switch these patients from their baseline medication to an appropriate dose of BDP. Please

We would appreciate your prompt written response so we can continue our evaluation of your supplemental NDA. If you have any questions, please contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

cc:
Original NDA 20-441
HFD-570/Div. Files
HFD-570/CSO/G.Trout
HFD-570/Meyer
HFD-570/Purucker
HFD-570/Elashoff
HFD-570/Wilson

Drafted by: gst/February 26, 1998

Initialed by: Schumaker/2-26-98
Elashoff/2-26-98
Wilson/2-26-98
Purucker/2-26-98
Meyer/2-26-98

INFORMATION REQUEST (IR)

Hilfike.

OCT -8 1998

Medical Team Leader Summary Review Memorandum

Application: 20-441, efficacy supplement S-002
Product: Pulmicort Turbuhaler
Memo date: 10-5-98

This memorandum is to document the secondary review conclusions on the efficacy supplement intended to establish the efficacy of once-daily dosing for the Pulmicort Turbuhaler, which is currently labeled for administration twice daily. The secondary review of the supplement was performed concurrently with Dr. Purucker's review. This memorandum, therefore, will only highlight some of the crucial efficacy review issues which form the basis of the finding that the application is approvable, provided revisions are agreed to in the proposed labeling.

Overview: The Pulmicort Turbuhaler was approved for marketing in June of 1997. Astra provided efficacy and safety data establishing the efficacy of budesonide administered in this device in a variety of asthma population subsets, including differing levels of severity, ages, and other demographic variables. The approval was for twice daily dosing in doses as low as 400 mcg daily (200 mcg BID) up to a total daily dose of 1600 mcg. This original NDA included data to attempt to establish the efficacy of once-daily dosing. However, the data were not convincing due to the choice of patients (very mild), the lack of a placebo group in many of the studies, and at least one adequate placebo-controlled study where 400 mcg QD was less effective than the same dose administered twice daily.

- Study 04-9050 was a study of Pulmicort 400 mcg once daily compared to placebo in non-ICS using chronic asthmatics. There was no difference in the primary outcome measure (clinic measured PEFR) in this 8 week trial.
- Study 04-2291 was a study of Pulmicort 400 mcg once daily (both AM and PM) compared to 200 mcg BID and placebo in steroid "naïve" patients. The primary variables were PEFR and symptom scores. This study showed the 400 mcg QPM and 200 mcg BID regimens to be effective relative to placebo by PEFR. However, only the 200 BID group separated from placebo in the symptom scoring and, in fact, beat the 400 mcg QPM dosing as well.
- Study 04-2292 was a Canadian study without placebo control examining the efficacy of 200 mcg BID compared to 400 mcg QD either administered in the AM or PM. This study failed to separate any of the doses, although numerically, the Q AM dose looked least effective. While all the means of all the treatments improved on airway measures and symptom scoring over the study, the interpretation of this change is made impossible by the lack of the placebo control.

These data offered little substantive assurance that once daily dosing was either effective or optimal for either initiating ICS therapy or for maintaining stability in asthma. Therefore, this claim was removed from the Dosage and Administration section of the

approved labeling.

This supplement, then, attempts to establish the efficacy of QD dosing for both corticosteroid naïve patients, as well as those receiving inhaled corticosteroids (ICS) prior to Pulmicort administration.

Efficacy: The primary evidence supplied by Astra in this supplement is study CR-0009, a large placebo controlled study of asthmatics who were both ICS users at entry and those in whom there was no recent ICS use. The study arms of this parallel study included doses of 200 and 400 mcg once daily, dosed in the morning, compared to placebo. Note that after a six-week "treatment" period, all patients were maintained on 200 mcg once daily for an additional 12 weeks. Overall, this study supports the efficacy of such a regimen in this population. However, there are several notable caveats to this conclusion:

1. There was no BID arm in this trial for comparison of relative efficacy, so while there was statistical separation of the once-daily dosing overall from the placebo group, it is not possible to state that the asthma control would be as good as with BID dosing.
2. This was a large trial with n > 100 patients per arm. This is larger than commonly needed to detect a treatment effect with ICS in asthma (i.e., smaller effects than commonly seen would be deemed "signficant" due to increase in power).
3. Even in the overall analysis, the sponsor did not win on both primary endpoints for the treatment phase for the 200 mcg daily dose, especially taking into account a conservative use of corrections for multiple endpoints (i.e., multiple doses, two primary endpoints, two study phases).
4. When a post-hoc analysis of the ICS naïve vs. ICS using population was reviewed (being originally requested by FDA), it became clear that the effect size in the ICS naïve patients was small (change in peak flow measures of around 7 L/min relative to placebo; change in FEV_1 of around 0.12 L) during the treatment phase, both of these less than half the relative difference seen in the ICS using group.
5. Although other supportive trials were submitted (including resubmission of trials discussed above), there were no other firm, substantive findings supporting the efficacy of once-daily dosing in the corticosteroid naïve population. This is added to by the fact that these studies were not performed with the US approved device.

Overall Conclusions: I am in agreement with Dr. Purucker's assessment that this application is approvable from the clinical standpoint, if the proposed Dosage and Administration recommendations are restricted to the use of once daily dosing as an alternative for patients previously receiving inhaled corticosteroids. Based on this pivotal study and other data available, there does appear to be reasonable data to support the efficacy of once daily dosing in maintaining asthma stability in some individuals.

However, given the uniqueness of this claim and the amount of contradictory data provided in this supplement and the original NDA, I do not feel that the weight of evidence is currently adequate to conclude that once daily dosing is safe and effective for initiation of therapy in corticosteroid naïve patients nor as a full treatment alternative for all patients.

Finally, with the advent of once daily dosing, it will be incumbent on all sponsors to address issues such as optimal timing (e.g., the relative efficacy of evening or morning) and relative systemic effects of once daily dosing compared to the more traditional split dosing regiments. We should request the sponsor, in particular, to address this issue as it relates to growth effects, since this is an increasingly important issue. For such a pharmacodynamic comparison of two or three dosing regimens (BID vs. QD a.m. vs. QD p.m.), use of a knemometry assessment over a short term would likely be sufficiently informative to address this question.

/S/

10/8/97

Robert J. Meyer, MD
Medical Team Leader
Division of Pulmonary Drug Products

CC: Purucker
~~Otulana~~/Medical Officer/HFD-570
Meyer/Medical Officer/HFD-570
Trout ~~Strange~~/CSO/HFD-570
Division File/HFD-570
NDA #20-441

APPEARS THIS WAY
ON ORIGINAL

HILF/22-L

LABELING REVIEW

OCT -8 1998

NDA #: 20-441/S-002
Drug: Pulmicort Turbuhaler (budesonide inhalation powder)
Applicant: Astra Pharmaceuticals, L.P.
Letter Date: October 6, 1997
Receipt Date: October 8, 1997
Provides for: Once daily dosing

After review of the original studies submitted on October 6, FDA concluded that there was sufficient evidence for once daily dosing for maintenance but not initiation of therapy. This conclusion was communicated in a telephone conversation with Astra on October 1, 1998, and FDA gave Astra two options. Either this application could be approved with limited claims given in the label and Astra could submit an additional efficacy supplement to support once daily dosing for initiation of therapy, or this application could be approvable (AE) until further information was submitted to substantiate once daily dosing for initiation. Astra elected for the former approach.

Therefore, FDA provided Astra with a marked-up copy of the package insert with our suggested changes via facsimile on October 1, 1998, and Astra submitted a revised package insert to the application on October 5, 1998. The October 5, 1998, package insert was reviewed against our October 1 marked-up package insert.

REVISIONS AS RECOMMENDED BY FDA

All revisions were identical to the recommended language in the FDA marked-up version of the package insert with one exception as follows:

Under DOSAGE AND ADMINISTRATION, FDA recommended that a footnote (denoted with an asterisk*) be included with the table to read, "In patients with mild to moderate asthma who are well controlled on inhaled corticosteroids, dosing with Pulmicort Turbuhaler 200 mcg or 400 mcg once daily may be considered, administered either in the morning or in the evening." In Astra's submission of revised labeling, the footnote reads, "...may be considered. PULMICORT TURBUHALER can be administered once daily either in the morning or in the evening."

This change is for grammatical purposes and does not change the recommended meaning, and is therefore acceptable.

ADDITIONAL REVISIONS NOTED BY ASTRA

Astra noted one additional revision related to an indication for once daily dosing that was not recommended by FDA. Under PRECAUTIONS, Information for Patients subsection, the first bullet originally read, "Patients should take the medication as directed and use

PULMICORT TURBUHALER at regular intervals [redacted] since its effectiveness depends on regular use." This statement was revised to read, "Patients should use PULMICORT TURBUHALER at regular intervals as directed since its effectiveness depends on regular use." This change is acceptable to accommodate the approval of once daily dosing for some patients.

ADDITIONAL REVISIONS NOT NOTED ELSEWHERE

Astra did not mention one additional difference between the FDA marked-up label of October 1 and Astra's revised label of October 5. Under HOW SUPPLIED, FDA's recommended labeling indicates that the wording [redacted] 200 mcg" should be printed on the grip. Astra's revised package insert indicates that "Pulmicort™ 200 mcg" is to be printed on the grip.

This change was recommended in a June 24, 1997, approval (AP) letter, and is therefore acceptable.

CONCLUSIONS

The October 5, 1998, proposed revised package insert should be approved.

David Hilfiker
Project Manager /S/ 10-15-98

APPEARS THIS WAY
ON ORIGINAL

POST-REVIEW ADDENDUM

Following this review, Bob Meyer, Clinical Team Leader, reviewed the October 5 revised package insert with Joan Hankin in the Division of Drug Marketing, Advertising, and Communications. Ms. Hankin commented that use of the terminology "asthma ( )" used in the CLINICAL TRIALS, Patients Receiving PULMICORT TURBUHALER Once Daily subsection, is not preferrable because of previous advertising claims that have been made from that phrase. Ms. Hankin recommended that the Division reconsider this terminology. Dr. Meyer proposed to replace "asthma ( )" with "asthma stability." I telephoned Dennis Bucceri, Astra Regulatory Affairs, and proposed this alternative. He accepted.

This revision will be noted in the approval letter as part of the approved revised draft package insert.

David Hilfiker
Project Manager /S/ 10-8-98

Cc: Original NDA 20-441/S-002
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Schumaker
HFD-570/Purucker
HFD-570/Meyer

/S/ 10-8-98

APPEARS THIS WAY
ON ORIGINAL

16 **Page(s) Redacted**

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