CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-093

CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service
Division of Cardio-Renal Drug Products

Memorandum

DATE : 7/19/00

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

SUBJECT: Approval of NDA 21-093, AstraZeneca, Candesartan/Hydrochlorothiazide

TO : NDA FIle

Introduction

This is a fixed dose combination product that incorporates two approved drugs, candesartan (an angiotensin II blocker) and hydrochlorothiazide (a diuretic) for the treatment of hypertension. The NDA furnished results form 19 clinical studies, that randomized 4588 patients for evaluation of efficacy, 1989 patients that received various doses of each agent, alone or together; a database of 6426 was evaluated for safety. Doses of candesartan from 4 to 32 mg and doses of hydrochlorothiazide from 6.25 to 25 mg were studied.

Candesartan is approved for monotherapy over a dose range of 2 to 16 mg a day in single or 2 divided doses. Hydrochlorothiazide is approved for monotherapy over a dose range of 25 to 50 mg once-a-day. The to be marketed formulation of candesartan/hydrochlorothiazide will have 2 strengths, 16 mg-12.5 mg and 32 mg-12.5 mg (candesartan/hydrochlorothiazide). This seems appropriate, since the combination product is to be used as a convenience dosage form. It will not be for initial therapy.

The combination of candesartan 32 mg and hydrochlorothizide 25 mg was not evaluated in any trial (placebo controlled or not. I do not regard that as a problem.

It is noted that a "bioequivalence" study that compares the to-be-marketed product the formulation used in one trial is not available. There is a comparison of the to-be-marketed formulation and the individual single entities. I do not find the one omission to be concerning. The blood pressure will be monitored when the product is used, and the product is clearly antihypertensive.

Major Trials

There were 5 major trials (SH-AHK-004, EC408, AM153, AM124, EC403), each randomized, placebo-controlled and including candesartan alone, hydrochlorothiazide alone, and the two in combination, that formed the basis of a pooled analysis that was evaluated as a single factorial trial in the Combined Medical/Statistical review written by Dr. Fredd and Mahjoob. Each trial separately and the pooled analysis unequivocally establish that each ingredient contributes to the combination's effect and that the antihyhpertensive effect increases as the dose of candesartan is increased from 4 to 32 alone or combination with hydrochlorothiazide over the dose range of 12.5 to 25 mg.

The pooled analysis utilized a quadratic model for generating a response surface. The exact shape of the curve should be ignored, since the quadratic model requires the calculated effect to decrease as dose (on either axis) increases. The shape does, however, clearly indicate that both ingredients contribute to the effect of the combination product ($p < 0.0001$). Ignoring the lack of a 32/25 does evaluation, the raw data show a decrease (placebo subtracted) of 8 to 10 mm Hg (standing systolic blood pressure arbitrarily picked for this citation) for both the 16/32 and 32/12.5 combination. Sitting diastolic blood pressure, for the same doses, was decrease by 7 to 9 mm Hg.

Of interest is Study EC 415 which randomized 23 hypertensive patients (diastolic >= 95 mm Hg) to 16 mg candesartan/25 mg hydrochlorothizide and measured the time course of blood pressure change as well as pharmacokinetics for a little more than 24 hours following the 1st dose. There were effects of the first dose and no

particular adversity was noted.

Potassium and QT_c

The use of hydrochlorothiazide was accompanied by a mean decrease in serum potassium. Since the doses of hydrochlorothiazide were 12.5 and 25 mg, the changes observed were small. Less mean change was observed with the use of placebo or the combination of candesartan and hydrochlorothiazide. Although the sponsor claims that 1% of patients treated with hydrochlorothiazide were reported to have had hypokalemia and only 0.4% of patients treated with the combination were reported to have had hypkalemia, there are no analyses that suggest the dose of candesartan was important to the phenomenon claimed and it is not clear that this is a real finding. Although, it is consistent with prior experiencial data (e.g., with irbesartan/hydrochlorothiazide).

There were no findings of import related to QT_c, although the review devotes a few pages to it.

Summary

Not surprisingly, the combination of candesartan and hydrochlorothiazide is an effective antihypertensive and out of the 6426 patients reported in the NDA, there were no safety issues of note. Certainly, provided physicians titrate over the approved dosage range of candesartan, there will be patients whose blood pressure is inadequately controlled and hydrochlorothiazide will need to be added to their regimens. Despite the prediction of the quadratic model, there is absolutely no reason to believe that (as the dose of candesartan increases in combination with hydrochlorothiazide) the antihypertensive effect of the combination decreases as a function of dose. Consequently, despite no actual experience in the NDA with a dose of 32/25, that particular dosage strength is approvable, many patients will be tritrated to those doses in practice by using approved single entities.

So, candesartan/ hydrochlorothiazide is approvable. The marked up package insert is on diskette.

AstraZeneca

Fax

To	Mr. Edward Fromm	**Fax number**	301-594-5494
Company	Food and Drug Administration		
From	AstraZeneca LP	**Fax number**	610-695-4492
Date	25 August, 2000; 11:02	**Total pages**	1(2)
Subject	Summary of August 24, 2000 Discussion Dissolution Methods and Specifications NDA 21-093		

CONFIDENTIAL

Mr. Fromm,

As requested during our telephone conversation yesterday, please find a summary of the discussion and the subject dissolution data.

During the August 24, 2000 telephone conversation AstraZeneca LP (AZLP) provided data indicating that seven of seven proposed commercial batches of 16+12.5 mg tablets tested with the FDA imposed method did not meet the specification at testing. Five of the seven batches failed testing. Finally, one of two batches tested at failed. This data is provided below in TABLE 1. The table also includes results from the testing time point as a comparison.

After discussing the above results, Dr. Marroum indicated that it was acceptable for AZLP to adopt a testing time point for the 16+12.5 mg tablet. In summary, the dissolution methods and specifications agreed on for candesartan cilexetil+hydrochlorothiazide 16+12.5 and 32+12.5 mg tablets are as follows:

AstraZeneca L.P.
725 Chesterbrook Blvd
Wayne, PA 19087

Tel +1 610 695 1000

AstraZeneca

To Mr. Edward Fromm Date 25 August 2000 Page 2(2)

CONFIDENTIAL

TABLE 1

Dissolution Testing of Candesartan Cilexetil in Candesartan Cilexetil+Hydrochlorothiazide 16+12.5 mg Tablets

Article No	Batch No	Sample No											
			Min	Max	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max	$\bar{x}$	Min	Max	$\bar{x}$
20-322-09	600101	66384/80472												
20-322-09	600201	66389/80482												
20-322-09	600301	66394/80484												
20-322-09	600401	66399/80515												
20-322-09	600601	66404/80516												
20-322-09	600701	66409/80517												
20-322-09	600801	67405/80758												

NT = not tested

Questions concerning this FAX can be addressed with me at (610) 695-4031.

Sincerely,

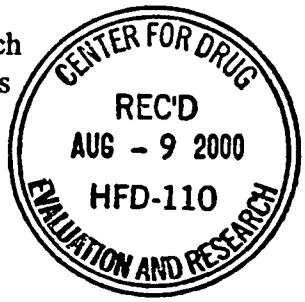
Len Alansky
Manager, CMC

cc: Ms. Cindy Lancaster (AZLP)

AstraZeneca
Cindy M. Lancaster, M.S., M.B.A.
Director
Regulatory Affairs

August 8, 2000

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Document Control Room, HFD-110
1451 Rockville Pike
Rockville, MD 20852



Dear Dr. Lipicky:

NDA 21-093
ATACAND HCT™ (candesartan cilexetil-hydrochlorothiazide) Tablets
Amendment to a Pending Application:
Chemistry, Manufacturing and Control

Reference is made to our original NDA 21-093 dated September 28, 1999. Reference is also made to the Division's approvable letter, dated July 19, 2000 and to a July 28, 2000 teleconference held with Drs. Marroum, Nguyen, and Srinivasachar.

As a result of the July 28 discussion, AstraZeneca LP is accepting the dissolution method and specification as proposed by the Division in the approvable letter. This submission contains the updated specifications and test methods for candesartan cilexetil+hydrochlorothiazide 16+12.5 and 32+12.5 mg tablets. These specifications and test methods will be implemented prior to commercial launch of the product.

We are also simultaneously providing a copy of this information to the Philadelphia District Office of the Food and Drug Administration.

AstraZeneca LP understands that the information contained herein, unless otherwise made public by AstraZeneca is confidential. Government agencies are not authorized to make it public without written permission from AstraZeneca LP.

Questions concerning this submission should be addressed to me at (610) 695-1348, or in my absence, to William McCanty, Regulatory Project Manager at (610) 578-8341 or Len Alansky, Product Industrialization/CMC at (610) 695-4031.

Sincerely,

Cindy M. Lancaster

Cindy M. Lancaster, M.S., M.B.A.
Director
Regulatory Affairs

1 Archival Original and 1 Review Copy
1 Copy of Cover Letter: Mr. Edward Fromm, RHPM, HFD-110

1 Desk Copy: Philadelphia District Office

Printed by Edward Fromm

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Mar-2000 04:53pm
From: Jerry Phillips
PHILLIPSJ
Dept: HFD-400 PKLN 15B03
Tel No: 301-827-3242 FAX 301-480-8173

TO: Edward Fromm (FROMME)

CC: Peter Honig (HONIGP)
CC: Sammie Beam (BEAMS)
Subject: OPDRA Consult 00-0011; ATACAND HCT

Ed:

Please consider this an official OPDRA response to your 1/4/00 consult request for review of the proprietary name ATACAND HCT (Candesartan cilexetil-hydrochlorothiazide). An Expert Panel Discussion recently met on this name and concluded that the name was satisfactory. Since ATACAND has already been previously approved and the HCT is commonly used with other combination products containing hydrochlorothiazide, we have no objection.

Thus, our recommendation:

OPDRA has no objection to the use of the proprietary name of ATACAND HCT for NDA 21-093. There will be no need to resubmit this name to \ prior to approval. This can be considered a final decision and firm can be so notified.

Thanks!

Jerry Phillips
Associate Director, OPDRA

APPEARS THIS WAY
ON ORIGINAL

AstraZeneca

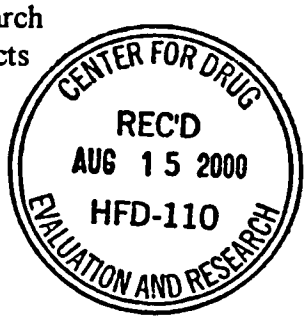
ORIGINAL

Cindy M. Lancaster, M.S., M.B.A.
Director
Regulatory Affairs

August 14, 2000

ORIG AMENDMENT
AF

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Document Control Room, HFD-110
1451 Rockville Pike
Rockville, MD 20852



Dear Dr. Lipicky:

NDA 21-093
ATACAND HCT™ (candesartan cilexetil-hydrochlorothiazide) Tablets
Amendment to a Pending Application
Response to FDA Approvable Letter: Final Printed Labeling

Reference is made to our original NDA 21-093, dated September 28, 1999, and to the Division's Approvable Letter, dated July 19, 2000, which contained a request for AstraZeneca LP to submit final printed labeling as a condition of approval for this NDA. Reference is also made to AstraZeneca's proposal, dated July 31, 2000, for revisions to the labeling and to a conversation with Mr. Edward Fromm on August 7, 2000, in which he informed AstraZeneca that the Division had accepted this proposal. In response to the request in the approvable letter for final printed labeling, AstraZeneca is hereby submitting 20 copies of the final printed labeling for NDA 21-093.

In addition, we are providing a marked-up copy of the labeling highlighting the agreed upon revisions and a copy of the clean running text as well. Furthermore, we are providing a copy of the package insert in PDF format on diskette (filename = ATACANDHCTPIFPL.pdf). Please also note that the package insert identification number and issue date will be filled in, after the Division issues the approval letter, at the time of first printing of this labeling.

MEMORANDUM

Date: 10 July, 2000

From: K. Srinivasachar, Ph.D., Chemistry Team Leader, HFD-110 /S/ 7-10-00

To: NDA 21-093, ATACAND HCT Tablets (candesartan cilexitil-hydrochlorothiazide)

Subject: Addendum to Chemistry Review #1 dated 27 June, 2000 by J. Piechocki

Review #1 lists three issues which need to be resolved before the application can be considered satisfactory from a CMC standpoint:

1) Lack of data to qualify a new lot of the reference standard for candesartan cilexetil.
2) -
3) Change in the dissolution specification for the 32/12.5 mg tablet strength based on the OCPB (Biopharm) recommendation.

Some other issues were identified during the secondary review and are listed below:

4) Lack of a release specification for water content in the drug product.
5) Lack of justification for the acceptance criterion of i for the hydrochlorothiazide degradation product, HU-1.
6) Recommendation to continue monitoring moisture levels and hardness of the tablets in stability studies on the first three commercial batches.

The firm was notified of these pending issues in a telephone conversation on June 22, 2000 and a response was received in the Amendment of June 30, 2000. These responses and an evaluation are summarized below for each of the six items :

1) The method of preparation and specifications for the new lot of reference standard are provided by reference to NDA 20-838 since candesartan cilexitil is the common active in both NDAs.

The impurity profile shows that none of the related substances is present at levels more than and the total is **Satisfactory**

2) data will be available before product launch and will be submitted in a General Correspondence to the NDA as soon as they are available. **Satisfactory.**

3) The recommendations on dissolution specifications are being conveyed to the firm separately
d are shown below:
adesartan cilexitil/HCTZ 16mg/12.5 mg:

AstraZeneca also makes further reference to our submission, dated August 8, 2000, regarding the dissolution method and specifications and to our previous commitments that were outlined in the approvable letter with regard to the Chemistry, Manufacturing and Controls information. Additional testing of tablets, to , will be performed for the combination product. Tablets of both strengths will be according to the ICH guideline.

AstraZeneca commits to report these data before launch as a "General Correspondence" to the NDA. AstraZeneca also commits to monitoring moisture and hardness on the first three commercial batches of both tablet strengths and, if these data are satisfactory, AstraZeneca will notify the Division by "General Correspondence" and obtain concurrence regarding our proposal to discontinue this testing on future annual batches.

It is our understanding that the information contained herein provides the Division with the final information needed to satisfy the approvable letter in order for the Division to approve NDA 21-093.

AstraZeneca understands that the information contained herein, unless otherwise made public by AstraZeneca is confidential. Government agencies are not authorized to make it public without written permission from AstraZeneca LP.

Questions concerning this letter should be addressed to me at (610) 695-1348, or in my absence, to William McCanty, Regulatory Project Manager at (610) 578-8341.

Sincerely,

Cindy M. Lancaster

Cindy M. Lancaster, M.S., M.B.A.
Director
Regulatory Affairs

1 Archival Original with 20 copies of final printed labeling
1 Review Copy
1 Copy of Cover Letter: Mr. Edward Fromm, RHPM, HFD-110
Professional Courier

4) The firm has argued that moisture content is adequately controlled in - process as a LOD test after granulation (. Time 0 values for water content in the tablets, as measured by Karl Fisher titration are in the range of but it is stated that the 2 methods are different and so the numerical values cannot be directly compared. It is further claimed that the stability data accrued so far do not show any correlation between degradation of HCTZ and water content. There is an increase in water content, for product in blister packages at after 6 months, of about for one batch and for another batch but the increase in HCTZ degradation products for both batches is the same.

Partially Satisfactory. The initial levels of water in the tablets are rather high , and additional information is needed to confirm that the in-process LOD test is actually able to control moisture levels in the finished product adequately.

5) The degradation product HU-1 (HCTZ diner) is not mentioned in the USP monograph but is in Ph.Eur. with a limit of The firm feels that a specification limit of is appropriate since HU-1 levels do increase with time especially under accelerated conditions. It is also claimed that this limit of at end of shelf life gives a lower exposure than tablets manufactured with HCTZ substance with the Ph.Eur. limit of 0.5 % when considering the daily dosing of HCTZ of up to 100 mg. AstraZeneca has committed to further review the limits for HCTZ related substances after more experience with industrial scale batches. **Satisfactory.**

6) The firm will monitor the first 3 commercial batches for moisture and hardness and will notify the Agency via Annual Report when they terminate these tests. **Partially Satisfactory. The notification should be by General Correspondence to the NDA rather than in an Annual Report to enable timely review of the data and Agency concurrence**

should be obtained before terminating these tests.

AstraZeneca was again contacted by telephone on July 5, 2000 regarding the partially satisfactory responses and another amendment dated July 7, 2000 was received in response.

Regarding the lack of a moisture content specification at release in the finished product:
The difference between the LOD in-process test results and the Karl Fisher Titration values at the initial time point in the stability studies was explained. The LOD test measures only loosely bound water whereas the Karl Fisher techniques accounts for all water in the sample including bound crystalline water. The in-process test was stated to adequately control water content in the final product based on the small variation in Karl Fisher results at time 0 in stability batches for both strengths. **Satisfactory**

Regarding notification of the discontinuation of moisture and tablet hardness testing based on satisfactory results on the first three commercial tablet batches:
The firm has made a commitment to report termination of these tests in a General Correspondence to the NDA rather than in an Annual Report. **Satisfactory.**

Conclusions and Recommendations: All CMC issues have been satisfactorily resolved. The NDA may be approved from the chemistry standpoint. Methods validation will be initiated shortly. The following statement should be included in the action letter to the Applicant:
You are reminded of your agreement to provide the results prior to product launch and your commitment to monitor moisture content and tablet hardness on the first three commercial batches and obtain Agency concurrence before terminating these tests on future annual batches.

CC:
Orig. NDA 21-093
HFD-110/ Div. File NDA 21-093
HFD-110/ KSrinivasachar/Project Manager/FZielinski
HFD-810/JSimmons

AstraZeneca
Cindy M. Lancaster, M.S., M.B.A.
Director
Regulatory Affairs

May 25, 2000

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Document Control Room, HFD-110
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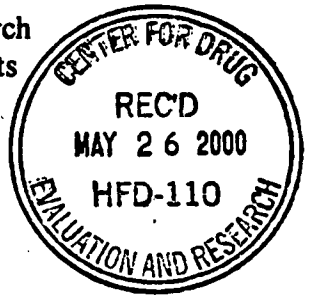
Rockville, MD 20852



Dear Dr. Lipicky:

NDA 21-093
ATACAND HCT™ (candesartan cilexetil-hydrochlorothiazide) Tablets
AMENDMENT TO A PENDING APPLICATION: RESPONSE TO FDA REQUEST
UPDATE of SAFETY INFORMATION

Reference is made to our original NDA 21-093, dated September 28, 1999, and to a request from Mr. Edward Fromm on May 18, 2000, about whether there were any updates of safety information planned, in accordance with 21 CFR § 314.50(d)(5)(vi)(b), by AstraZeneca LP. The purpose of this correspondence is to inform the Division that all safety data has been submitted either in the original NDA or in subsequent amendments and confirm that there are no new safety data that may reasonably affect the labeling. Presently, there are no on-going controlled or open-label studies of candesartan cilexetil-hydrochlorothiazide tablets in patients with hypertension. Consequently, AstraZeneca does not have any additional "Safety Update Reports" planned for candesartan cilexetil-hydrochlorothiazide tablets.

AstraZeneca understands that the information contained herein, unless otherwise made public by AstraZeneca is confidential. Government agencies are not authorized to make it public without written permission from AstraZeneca.

Questions concerning this submission should be directed to me at (610) 695-1348 or by facsimile at (610) 695-1828, or in my absence, to William McCanty, Regulatory Project Manager at (610) 578-8341.

Sincerely,

Cindy M. Lancaster

Cindy M. Lancaster, M.S., M.B.A.
Director, Regulatory Affairs

Attachment

1 Archival Original and 1 Review Copy
1 Desk Copy: Mr. Edward Fromm, RHPM, HFD-110