CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S12

CORRESPONDENCE

NDA SUPPL FOR SCM

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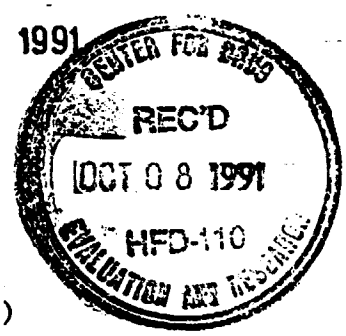
OCT 8 1991



Gentlemen:

Re: ZESTRIL® (lisinopril)
NDA 19-777
ZESTORETIC® (lisinopril/hydrochlorothiazide)
NDA 19-888

The purpose of this submission is to provide for the contract manufacture of 2 reaction intermediates isolated during the synthesis of the TFA-lisinopril ester. TFA-lisinopril ester is an alternative pivotal intermediate approved by the Agency for use in the manufacture of lisinopril dihydrate. The Applicant offers the following information/data in support of this supplemental New Drug Application (sNDA).

Attachment 1 contains the November 9, 1990 correspondence approving the February 14, 1990 submission to the ZESTRIL® (lisinopril) NDA (NDA 19-777) providing for the manufacture of TFA-lisinopril ester by . Also included is the December 21, 1990 correspondence approving the December 7, 1990 submission to the ZESTORETIC® (lisinopril/hydrochlorothiazide) NDA (NDA 19-888) which provided for the use of the TFA-lisinopril ester manufactured by .

Attachment 2 includes the TFA-lisinopril ester nomenclature and synthetic route from the February 14, 1990 submission. The Applicant proposes to will be purchased from outside contractors. The contractors synthesize the by identical routes described in this Attachment.

Attachment 3 provides for the known impurities arising from the methods of manufacture contained within the February 14, 1990 submission. Also included are the specifications and test methods for the control of these intermediates. The latter information is from the June 20, 1990 amendment (pp. 114-119) to the approved February 14, 1990 sNDA.

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Attachment 4 includes the specifications for the prepared by the contractors. The attached specifications are equal to or greater than those contained in the approved sNDA. In addition to specifications also include limits on the related compounds cis-isomer and ethyl β-benzoyl-α-ethoxypropionate, heavy metals (as lead) and arsenic. The proposed chemical purity specification for (has been tightened from the approved %.

Attachment 5 includes analytical data on 3 pilot-scale lots of the manufactured by the contractor. These data are compared to that from a full-scale production of 1 lot of the same intermediates manufactured by

Attachment 6 contains the specifications and test methods for the TFA-lisinopril ester provided for in the approved February 14, 1990 sNDA. The test methods and specifications for the TFA-lisinopril ester manufactured via the proposed, route are unchanged from those approved on November 9, 1990.

Attachment 7 provides analytical data on 1 batch of the TFA-lisinopril ester using from contractors as starting materials.

Attachment 8 contains a copy of the letter notifying the Applicant that is changing their name to effective September 1, 1991.

The Applicant believes that the data presented in this submission clearly indicates that the quality of the TFA-lisinopril ester is uncompromised when manufactured by the route. The Applicant would appreciate an expeditious review of the submission.

If you should require any further clarification or information, please do not hesitate to contact me.

Sincerely,

Kevin McKenna

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KM/mjb

Desk Copy: Dr. James H. Short, HFD No. 110, Room No. 16-B19