CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19777/S11

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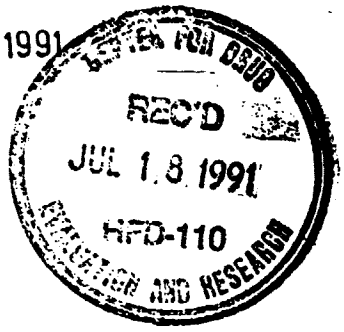

Gentlemen:

Re: ZESTRIL® (lisinopril)
NDA 19-777
Rework Procedure

The purpose of this submission is to enable the sponsor to distribute two lots of ZESTRIL® (lisinopril) Tablets 10 mg which were manufactured subject to the approved rework procedure contained in the sponsor's approved New Drug Application. On January 18, 1989, a supplemental application providing a rework process for ZESTRIL Tablets 10 and 20 mg using up to % rework material was approved. The approval of this supplement provided for the use of nonvirgin material which was not more than one year old. However, a one-time exemption was allowed by the Agency enabling the sponsor to rework existing material which was more than one year old.

In September 1990, the sponsor prepared an intermediate granulation (Lot 1215K) of nonvirgin material to be included in rework tablets to a maximum of % of this granulation. The total amount of intermediate granulation was kg. The oldest component of this nonvirgin granulation was regrind material from one tabletted batch (Lot 9016K, manufactured in March 1990). This intermediate granulation should have been assigned a "do not use after" date of March 1991. Inadvertently, a "do not use after" date of June 1991 was assigned. This regrind material made up kg or % of the total intermediate granulation Lot 1215K. Subsequently in June 1991, two batches of ZESTRIL Tablets 10 mg (Lots 7032LR and 7033LR) were produced by the sponsor using intermediate granulation Lot 1215K. The percentages of recovery material from intermediate granulation Lot 1215K in these two lots were % in Lot 7032LR and % in 7033LR. Therefore, the percentages of material older than one year (Lot 9016K, manufactured in March 1990) used in these two lots were only % and %, respectively.

This inadvertent error was discovered prior to the final Quality Assurance release and distribution of these lots.

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The process used for the production of these lots was exactly that provided for in the supplemental application approved on January 18, 1989.

The intermediate granulation (Lot 1215K) was tested in September 1990 and reassayed in April 1991 and was found to meet all specifications. The two ZESTRIL Tablet 10 mg lots (Lot 7032LR and 7033LR) were tested following their manufacture, and both were found to meet all specifications.

In support of this submission, the following attachments are provided:

- Exhibit 1 - The Certificates of Analysis setting out the release testing results for tabletted Lots 7032LR and 7033LR
- Exhibit 2 - Certificates of Analysis setting out the testing results for intermediate granulation Lot 1215K performed in September 1990 and a Certificate of Analysis for the reanalysis of that batch in April 1991
- Exhibit 3 - Copy of the stability data contained in the sponsor's stability program for ZESTRIL Tablets filed with the most recent Annual Report (July 1991). Lot 4412J, in this report, represents a rework batch which used rework material more than one year old manufactured under the original Agency allowance.

The sponsor is now requesting approval for these reworked lots (7032LR and 7033LR). The sponsor will calculate the expiry date for the subject batches from March 1990, which is the date of the oldest material. The sponsor will also place both lots in its commercial stability program and will promptly withdraw from the market these lots if they do not meet their existing specifications throughout their assigned shelf life.

The stability data indicates no significant differences between this reworked batch and batches made totally of virgin material.

The sponsor wishes to reiterate that the production of these two batches resulted from an inadvertent error, and steps have been taken to ensure that this situation will not reoccur.

If you require additional information, please do not hesitate to contact me.

Sincerely,

Robert Castor
Manager
Technical Regulatory Affairs and Compliance
Drug Regulatory Affairs Department
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RC/mjb
Attachments