CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S014

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December 12, 1996

NDA NO. 19-787 REF. NO. 014
NDA SUPPL FOR SCS

Raymond Lipicky, M.D., Director
Division of Cardio-Renal
Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
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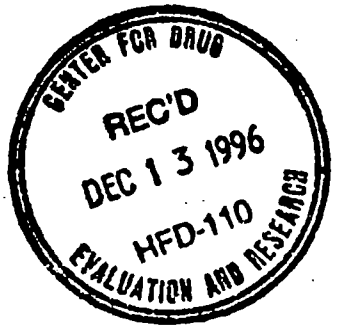

RE: Norvasc (amlodipine besylate) Tablets
NDA # 19-787
Supplemental Application

Dear Dr. Lipicky;

Pursuant to CFR 314.70 (b)(1)(iv), we are submitting a supplemental application to Norvasc (amlodipine besylate) tablets, NDA #19-787.

The purpose of this supplement is to obtain approval for a change in of the amlodipine besylate manufacturing process. The currently approved process for manufacturing amlodipine besylate drug substance is process, where includes synthesis. This supplement requests approval of a process change that expands the allowable temperature ranges for this ether formulation.

The currently approved process requires that the reaction temperature in be held below °C during the addition of After the addition is complete, the reaction is stirred initially a °C and then at °C for at hours. The proposed process change described in this supplement would allow the addition of to occur at temperatures up to °C, with the subsequent reaction temperature allowed to occur at up to °C with a minimum reaction time hour. Laboratory and pilot scale work have demonstrated that the increased addition and reaction temperatures provides for a faster reaction which completed in a shorter amount of time. There are no process changes in

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Analytical data for amlodipine besylate drug substance manufactured using
show that the quality is comparable to drug substance manufactured according to the currently-approved process. There is no change in the impurity profile of the finished drug substance as a result of this process change, and the chemistry, synthetic route, and finished drug substance specifications are unchanged.

This supplement contains the currently approved process description for amlodipine besylate

Analytical data for the three batches of amlodipine besylate drug substance manufactured with
provided in the supplement, along with analytical data for one control batch of amlodipine besylate manufactured according to the currently approved process (Appendix III). The currently approved finished drug substance specification for amlodipine besylate is also provided for reference (Appendix IV).

One lot of amlodipine besylate drug substance manufactured according to the proposed process change will be placed into the long-term drug substance stability program.

If you have any questions regarding this supplement, please call my office at (212) 573-2503.

Sincerely,

I. Kissen

Inna Kissen, Ph.D.

IK:amw
Enclosure
NORVASC1/11

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.