CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19787/S022

APPROVAL LETTER

DEC 15 1999

NDA 19-787/S-022

Pfizer Inc.
Attention: Jean Lyons, MS
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Lyons:

Please refer to your supplemental new drug application (NDA) dated August 27, 1999, received August 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) Tablets, 2.5 mg, 5.0 mg and 10.0 mg.

The supplemental application provides for a rework procedure for amlodipine besylate blend for tablets which allows additional blending and comminution steps and incorporation of additional magnesium stearate %), if required.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

/S/ 12-15-99

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDCI
Division of Cardio-Renal Drug Products (HFD-110)
Office of New Drug Chemistry
Center for Drug Evaluation and Research

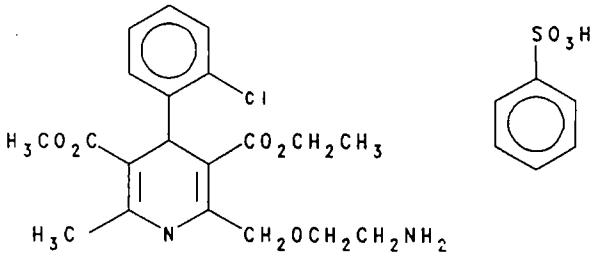
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S022

CHEMISTRY REVIEW(S)

DEC 14 1999

NDA 19-787/S-022 PFIZER NORVASC

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 19-787
3. Name and Address of Applicant (City & State) Pfizer, Inc. 235 East 42nd Street New York, NY 10017-5755		4. Supplement(s) Number(s) S-022 Date(s) 08-27-99
5. Drug Name NORVASC	6. Nonproprietary Name Amlodipine Besylate	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: (Prior Approval Supplement) a rework procedure which allows additional blending and comminution step for amlodipine besylate blend for tablets and incorporation of additional lubricant %).		Fax 12-13-99
9. Pharmacological Category Antihypertensive and Antianginal	10. How Dispensed /x/ RX /__/ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet	13. Potency(ies) 2.5, 5, and 10 mg	
14. Chemical Name and Structure 3-Ethyl-5-methyl-2-(2-aminoethoxymethl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonic acid 		15. Records/Reports Current /x/ Yes /__/ No Reviewed /x/ Yes /__/ No
16. Comments:		
17. Conclusions and Recommendations: Satisfactory and recommended for approval.		
18. REVIEWER		
Name Ramsharan D. Mittal	Signature /S/	Date Completed 12/14/99
19. Distribution: /__/ Original Jacket /__/ Reviewer /__/ Division File /__/ CSO		

/S/
12-14-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S022

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 12 1999

Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787
Serial # SCS-022
Norvasc (Amlodipine besylate) Tablets 2.5, 5, and 10 mg
Pfizer Pharmaceuticals Group
Submission Date: August 27, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Request for Approval of a Rework Procedure for Norvasc Tablets

BACKGROUND

The sponsor has submitted a request for an approval of a new manufacturing procedure for Norvasc Tablets. The rework procedure for amlodipine besylate blend for tablets allows for additional blending and comminution steps in the manufacturing process. The sponsor believes this rework will achieve more acceptable product blend characteristics. The rework also allows for the incorporation of additional lubricant % magnesium stearate) if required. The sponsor intends to utilize this rework procedure for blends with lumping, powder flow, compressibility, or blend uniformity issues as they arise.

The sponsor has manufactured three batch lots using the newly reworked processes. The sponsor tested each of the three lots and found that each complied with the sponsor's Specification-R's for each dosage form. The sponsor has provided batch records and certificates of analysis for these lots. The sponsor has also submitted stability data as well as a stability commitment and protocol for commercial production of the rework procedure if approved.

The sponsor submitted multi-point dissolution profiles for the rework batches using the currently approved dissolution methodology. For comparison, the sponsor also submitted dissolution profiles from commercial tablet batches. These profiles are included in this review as Attachment 1. The sponsor believes the data supports the approval of the rework procedure for amlodipine besylate blend for tablets. The rework process as submitted by the sponsor is shown in Attachment 2.

COMMENTS

RECOMMENDATION

The rework blend for amlodipine besylate tablets is approvable. The sponsor has satisfied the test documentation required under the SUPAC-IR Guidance. The sponsor has demonstrated the similarity in dissolution profiles, for all marketed tablet strengths of amlodipine, between the currently approved commercial batches and batches of the proposed rework blends.

Please forward Comments 1-3 and this Recommendation to the sponsor in writing.

/S/

Thomas A. Parmelee, Pharm.D. 10/12/99

RD/FT by R. Baweja, Ph.D. /S/ 10/12/99

CC: NDA 19-787, HFD-110, HFD-860 (Mehta, Baweja, Parmelee), CDER document room: Attn. BIOPHARM CDR

ATTACHMENT 1

Table 1

Calculated Similarity Factors[1] (f_2) for Dissolution of Amlodipine Besylate Tablets

	Lot Numbers		
Strength (mg)	**Commercial**	**Reworked**	**f_2**
2.5	6QP130E-05725	N5121-QC3070	72
5	M596-05750	N5122-QC3071	76
10	6QP140-05770	N5123-QC3072	70

[1] Similarity factors were calculated using the following equation:

$$f_2 = 50 \log \left[\left(1 + 1/n \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} (100) \right]$$

where: n = number of time intervals
R_t = the average percent of active in the commercial lot dissolved at each time interval
T_t = the average percent of active in the reworked lot dissolved at each time interval

An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

Table 2 Dissolution Rates of Amlodipine Besylate Tablets, 2.5 mg (Lot 6QP130E-05725) Commercial

	Dissolution (% LC)				
Tablet	15 min	30 min	45 min	60 min	120 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	91	94	95	95	95
Std. Dev.	4.39	1.78	2.06	1.98	1.65
Low					
High					

Table 3 Dissolution Rates of Amlodipine Besylate Tablets, 2.5 mg (Lot N5121-QC3070) Reworked

	Dissolution (% LC)				
Tablet	15 min	30 min	45 min	60 min	120 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	83	94	95	95	95
Std. Dev.	5.67	1.95	3.18	2.76	1.85
Low					
High					

Commercial

Table 4 Dissolution Rates of Amlodipine Besylate Tablets, 5 mg (Lot M596-05750)

	Dissolution (% LC)				
Tablet	**15 min**	**30 min**	**45 min**	**60 min**	**120 min**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	90	94	96	95	96
Std. Dev.	6.60	2.42	1.62	1.16	2.22
Low					
High					

Table 5 Dissolution Rates of Amlodipine Besylate Tablets, 5 mg (Lot N5122-QC3071) Reworked

	Dissolution (% LC)				
Tablet	**15 min**	**30 min**	**45 min**	**60 min**	**120 min**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	92	92	92	94	92
Std. Dev.	1.47	1.98	1.61	2.23	1.87
Low					
High					

Table 6 Dissolution Rates of Amlodipine Besylate Tablets, 10 mg (Lot 6QP140-05770) Commercial

	Dissolution (% LC)				
Tablet	**15 min**	**30 min**	**45 min**	**60 min**	**120 min**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	93	93	93	94	94
Std. Dev.	1.51	1.24	1.04	0.94	1.67
Low					
High					

Table 7 Dissolution Rates of Amlodipine Besylate Tablets, 10 mg (Lot N5123-QC3072) Reworked

	Dissolution (% LC)				
Tablet	**15 min**	**30 min**	**45 min**	**60 min**	**120 min**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	98	97	97	97	97
Std. Dev.	2.56	2.07	1.78	2.07	2.48
Low					
High					

ATTACHMENT 2

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S022

CORRESPONDENCE

ORIGINAL

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 5999 Fax 212 573 1563
Email lyonsj@pfizer.com

Pfizer Pharmaceuticals Group

August 27, 1999

Jean Lyons, MS
Director
Regulatory Affairs

Raymond Lipicky, M.D., Director
Division of Cardio Renal Products (HFD-110)
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 19-787 REF NO. 022
NDA SUPPL FOR SCS

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

Dear Dr. Lipicky:

Please refer to Pfizer Inc.'s approved New Drug Application for Norvasc (amlodipine besylate) Tablets, NDA #19-787.

Pursuant to 21 CFR 314.70, Pfizer submits this supplemental application to NDA #19-787 to request approval of a rework procedure for Norvasc. Contained within this supplemental application is the proposed rework procedure, release requirements, stability, and dissolution data for both tablets and blend to support this request.

The currently approved Norvasc commercial dosage forms are 2.5, 5 and 10 mg tablets, approved by the FDA in a letter dated July 31, 1992. Pfizer incorporates the relevant portions of NDA #19-787 in this submission by reference.

Pfizer commits to place the first three commercial lots into our ongoing stability program, to periodically submit the stability data as it becomes available, and to withdraw from the market any lot that fails to meet the required specifications.

Additionally, as required by 21 CFR 314.70(a), a field copy of this supplemental application has been provided to Pfizer's home FDA district office.

Should you have any questions regarding this submission, please do not hesitate to contact me at (212) 733-5999.

Please include this supplement in the subject file.

Sincerely,

Jean Lyons

Enclosure

Field Copy
Desk Copy: David Roeder

ORIGINAL