CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-108

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

1. CHEMISTRY REVIEW NO.
4

2. ANDA
75-108

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Paragraph IV Certification: See Chemistry Review No. 2.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine,

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
4/7/97 - Original.
5/19/97 - Response to refuse to file.
5/21/97 - Response to refuse to file.
5/27/97 - Response to phone memo 5/23/97, (not in ANDA file), regarding inactive.
7/25/97 - O/NC, notification received, 21 CFR 314.95©.
9/17/97 - O/NC, response to phone call of 9/11/97, (not in ANDA file) from Dr. Thomas Papoian, HFD-110, regarding inactives.
9/25/97 - Amendment, safety evaluation of inactives referred to in 9/17/97, O/NC.
10/31/97- Response to BIO deficiency letter.
11/7/97 - Response to phone call of 11/3/97, (not in ANDA file) from HFD-110, regarding inactives.
12/8/97 - BIO information.
2/16/98 - NC, regarding inactive.
3/12/98 - Response to Chemistry/Labeling NA FAX #1 (Subject

of review #2).
4/21/98 - Labeling Amendment.
9/10/98 - Chemistry Amendment.
1/5/99 - Chemistry Telephone Amendment.
6/1/99 - NC, Ongoing litigation.
10/14/99- Amendment.
12/3/99 - Amendment (**Subject of this review**).
FDA:
5/12/97 - Refuse to file, inactive ingredient questions.

6/27/97 - Acknowledgment.

7/18/97 - Notification from Pfizer (NDA holder) filing legal action for patent infringement.
9/29/97 - Consult memo; Acceptable.
10/15/97- BIO NA letter.
2/12/98 - Chemistry/Labeling NA FAX.
4/13/98 - Labeling NA FAX.
3/15/99 - Tentative approval.
12/2/99 - FAX

10. PHARMACOLOGICAL CATEGORY
Antianginal

11. R_x or OTC
R_x

12. RELATED IND/NDA/DMF(s)
See Chemistry Review #2.

13. DOSAGE FORM
Extended-release Tablets

14. POTENCY
30 mg

15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP
$C_{17}H_{18}N_2O_6$
M.W. = 346.34
Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.
CAS [21829-25-4]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Amendment dated 12/3/99: This responds to our FAX dated **12/2/99**, which addressed FDA laboratory personnel observations of the methodology for the drug product, and asked for the available

stability data for the new exhibit batch (discussed in the **6/1/99**, amendment) that was manufactured to support Mylan's position in the on-going patent litigation w/Pfizer. See items 29. and 31. of this review.

Expiration of the 30-month period from the date of acknowledgement of the original submission will occur on **12/16/99**, and Mylan previously requested final approval of the ANDA in their **10/14/99**, amendment.

18. CONCLUSIONS AND RECOMMENDATIONS
Refer to T. Ames for final Approval.

19. REVIEWER
Robert C. Permisohn
/S/

DATE COMPLETED
12/7/99
12/14/99

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releasable.

Chemistry Review #4.

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

1. CHEMISTRY REVIEW NO.
3

2. ANDA
75-108

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Paragraph IV Certification: See Chemistry Review No. 2.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine,

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm: 4/7/97 - Original.
5/19/97 - Response to refuse to file.
5/21/97 - Response to refuse to file.
5/27/97 - Response to phone memo 5/23/97, (not in ANDA file), regarding inactive.
7/25/97 - O/NC, notification received, 21 CFR §314.95(c).
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12/8/97 - BIO information.
2/16/98 - NC, regarding inactive.
3/12/98 - Response to Chemistry/Labeling NA FAX #1 (Subject of review #2).
4/21/98 - Labeling Amendment
9/10/98 - Chemistry Amendment

1/5/99 - Chemistry Telephone Amendment
6/1/99 - NC, Ongoing litigation (**Subject of this review**).
10/14/99- Amendment (**Subject of this review**).

FDA: 5/12/97 - Refuse to file, inactive ingredient questions.
6/27/97 - Acknowledgment.
7/18/97 - Notification from Pfizer (NDA holder) filing legal action for patent infringement.
9/29/97 - Consult memo; Acceptable.
10/15/97- BIO NA letter.
2/12/98 - Chemistry/Labeling NA FAX.
4/13/98 - Labeling NA FAX.
3/15/99 - Tentative approval.

10. PHARMACOLOGICAL CATEGORY
Antiangina

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See Chemistry Review #2.

13. DOSAGE FORM
Extended-release Tablets

14. POTENCIES
30 mg

15. CHEMICAL NAME AND STRUCTURE
Nifedipine USP
$C_{17}H_{18}N_2O_6$
M.W. = 346.34
Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.
CAS [21829-25-4]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
NC dated **6/1/99**: This NC entitled "NEW CORRESPONDENCE PROVIDING CLARIFICATION TO ONGOING PATENT LITIGATION" is "NAI" per H. Greenberg on **6/3/99**. The applicant states that they do not believe that the information contained therein represents new information that is relevant or would be required to be submitted to their tentatively approved application. However, there is supportive data that is pertinent to the manufacture and stability of the drug product that requires attention. See sections 25. and 29. of this review.

Amendment dated 10/14/99: This refers to the patent litigation w/Pfizer and its impact on the final approval of this ANDA. The 30-month period from the date of acknowledgement of the original submission and instructions in the tentative approval letter dated **3/15/99**, are cited. Expiration of the 30-month period will occur on **12/16/99**, and Mylan requests final approval of the ANDA.

18. CONCLUSIONS AND RECOMMENDATIONS
Refer to T. Ames for final Approval and transmission of the FDA laboratory comments.

19. REVIEWER
Robert C. Permisohn
/S/

DATE COMPLETED
11/29/99
12/2/99

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Chemistry Review #3

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ADDENDUM TO ANDA REVIEW NO. 2

1. CHEMISTRY REVIEW NO.
   2 Addendum

2. ANDA
   75-108

3. NAME AND ADDRESS OF APPLICANT
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   P.O. Box 4310
   Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
   Paragraph IV Certification: See Chemistry Review No. 2.

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Nifedipine,

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   N/A

9. AMENDMENTS AND OTHER DATES:
   Firm:
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   - 7/25/97 - O/NC, notification received, 21 CFR §314.95(c).
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12/8/97 - BIO information.
2/16/98 - NC, regarding inactive.
3/12/98 - Response to Chemistry/Labeling NA FAX #1 (Subject of review #2).
4/21/98 - Labeling Amendment **(Subject of this review).**
9/10/98 - Chemistry Amendment **(Subject of this review).**
1/5/99 - Chemistry Telephone Amendment (**Subject of this review**).

FDA:
5/12/97 - Refuse to file, inactive ingredient questions.
6/27/97 - Acknowledgment.
7/18/97 - Notification from Pfizer (NDA holder) filing legal action for patent infringement.
9/29/97 - Consult memo; Acceptable.
10/15/97- BIO NA letter.
2/12/98 - Chemistry/Labeling NA FAX.
4/13/98 - Labeling NA FAX.

10. PHARMACOLOGICAL CATEGORY
Antiangina

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
See Chemistry Review #2.

13. DOSAGE FORM
Extended-release Tablets

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15. CHEMICAL NAME AND STRUCTURE

Nifedipine USP

$C_{17}H_{18}N_2O_6$

M.W. = 346.34

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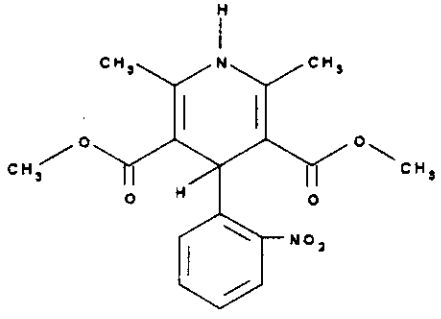
CAS [21829-25-4]



16. RECORDS AND REPORTS

N/A

17. COMMENTS

4/21/98, Amendment: FPL insert labeling Satisfactory per A. Vezza review dated **4/24/98** (see item 32).

9/10/98, Amendment: Spec. addition for the micronized ds intermediate (see item 23.A.)

The DOB review dated **12/23/98**, of the **10/31/97, amendment** recommended dissolution specs. that coincided with those proposed in the amendment. At that time, the applicant had also included in the same submission, revised Finished Product Specifications, and a revised Stability Protocol. Upon comparing the the DOB recommended specs. and those of the applicant, and the revised Finished Product Specifications and Stability Protocol with the previously submitted documents, this reviewer observed an error in the spec. for moisture content in the Stability Protocol which was probably due to a typographical error. T. Ames addressed this in a telecon on **1/5/99**, with the applicant.

1/5/99, Telephone Amendment: This responds to a telecon held on **1/5/99**, between the applicant and T. Ames as above. The moisture content spec. in the corrected Stability Protocol is consistent with that which was previously submitted.

Finished product method validation pending.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Approval - Pending MV.

19. REVIEWER
Robert C. Permisohn
/S/

DATE COMPLETED
1/8/99
1/7/99

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Christy Review

#2 addendum

1. CHEMISTRY REVIEW NO. 1

2. ANDA 75-108

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Paragraph IV Certification:
Pursuant 505(j)(2)(A)(vii) of FD&C Act, the applicant certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 5,264,446 (11/23/10); 4,783,337 (9/16/03); 4,765,989 (6/16/03); 4,612,008 (9/16/03) and 4,327,725 (11/25/00) are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Nifedipine ER Tablets, 30 mg, for which this application is submitted and that the referenced listed product is not covered by any exclusivity.
Pursuant 505(j)(2)(B)(I) of FD&C Act, applicant will provide notice to owners of above patents, or their representatives, and holder of approved NDA. Notice will comply with 21 CFR §314.99© for content and will be sent when acknowledgment letter accepting ANDA for filing is received as set forth in 21 CFR §314.95(b). Applicant commits to amend application to provide certification that notification was received as required by 21 CFR §314.95(e).

Innovator: Pratt Pharmaceuticals, Division of Pfizer, Inc. - Procardia XL® Tablets

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nifedipine,
Extended Release

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm: 4/7/97 - Original. Subject of this review.
5/19/97 - Response to refuse to file. Subject of this review.
5/21/97 - Response to refuse to file. Subject of this review.
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FDA: 5/12/97 - Refuse to file, inactive ingredient questions.
6/27/97 - Acknowledgment.
7/18/97 - Notification from Pfizer (NDA holder) filing legal action for patent infringement.

10. PHARMACOLOGICAL CATEGORY
Antiangina

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCIES
30 mg

15. CHEMICAL NAME AND STRUCTURE
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$C_{17}H_{18}N_2O_6$
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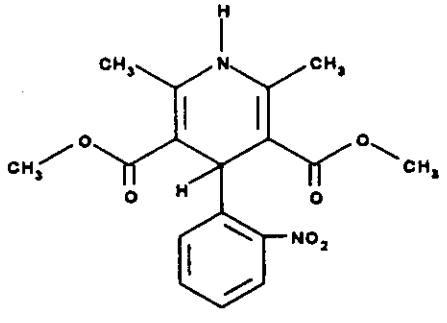
CAS [21829-25-4]



16. RECORDS AND REPORTS
N/A

17. COMMENTS
a. Inactive Ingredients:
(1) Monograph for changed in Third Supplement, also need to test for Loss On Drying and Monomers.
(2) Monograph for Polysorbate hanged in Third Supplement.
b. Manufacturing and Processing:
Remove the overage of active.
c. Laboratory Controls (Finished Dosage Form):
Dissolution specifications pending approval from Bio.
d. Stability:
Dissolution specifications pending approval from Bio.
e. Finished product method validation pending Bio. acceptance of dissolution method.
f. Labeling **pending review.**
g. Establishment Inspection request sent 5/2/97, pending.
h. Bio. assigned to Hoainhon Nguyen on 6/5/97, pending.

DMF acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (see item 17)

19. REVIEWER: Norman Gregory
DATE COMPLETED: 10/15/97

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Chemistry Review

FEB 12 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-108 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Nifedipine Extended-Release Tablet, 30 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Regarding Inactive Ingredients:

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research