CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74910

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-910 DRUG PRODUCT: Diltiazem Hydrochloride USP

FIRM: Mylan
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

DOSAGE FORM: HG Capsule

STRENGTHS: 60 mg
90 mg
120 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 5176) and Section 306(k) certification (p. 4)in original submission.

EIR acceptable for drug product manufacturer and drug substance manufacturer, 9/11/96.

Facilities included:

Manufacturing, testing, packaging, labeling, and stability testing:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, West Virginia 26505-2730

Drug Substance Manufacturer:

BIO STUDY:

Bioequivalence study conducted on the 120 mg capsules Lot #2B005L, batch size capsules, was found acceptable by the Division of Bioequivalence per M. Park, 10/28/96.

In-vitro dissolution testing results found acceptable, USP 23 Drug Release Test Type 4.

Waiver granted for the 60 mg and 90 mg products as they have been shown to be proportional to the 120 mg product.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance and drug product are compendial.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

Dosage	Lot #	Batch Size	Sample	Test Conditions
60 mg	2B003L		100's	40°C/75% RH/3 months 25° - 30°C/12 months
90 mg	2B004L		100's	40°C/75% RH/3 months 25° - 30°C/12 months
120 mg	2B005L		100's	40°C/75% RH/3 months 25° - 30°C/12 months

Container/Closure system:

60 mg/capsule - 100's in 75 cc round, beige HDPE plastic form bottle, 38 mm beige child-resistant closure, 100 innerseal/liner, cotton coil.

90 mg/capsule - 100's in 120 cc round, beige HDPE plastic form bottle, 38 mm beige child-resistant closure, 100 innerseal/liner, cotton coil.

120 mg/capsule - 100's in 120 cc round, beige HDPE plastic form bottle, 38 mm beige child-resistant closure, 100 innerseal/liner, cotton coil.

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, J. White, 2/21/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio batch: 120 mg product, Lot #2B005L, batch size capsules, stability data included.

Bio waiver requested for 60 mg product, Lot #2B003L, batch size capsules, and 90 mg product, Lot #2B004L, batch size capsules, stability data included.

DMF satisfactory, G.J. Smith, 11/19/96, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Executed batch records for the Intermediate Beads (kg), the Extended Release Beads (kg), the 60 mg x capsule batch (stability), the 90 mg x capsule batch (stability), and the 120 mg x capsule batch (bio/stability batch) included. Blank batch records were submitted in the application as follows:

Diltiazem HCl Intermediate Beads -	kg and	kg.
Diltiazem HCl Extended Release Beads -	kg and	kg.
60 mg capsules -	capsules and	capsules.
90 mg capsules -	capsules and	capsules.
120 mg capsules -	capsules and	capsules.

All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST: /S/ DATE: 3-24-97

SUPERVISOR: /S/ DATE: 3/25/97

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-910

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
Cardizem® SR Capsules, 60 mg, 90 mg, 120 mg
Hoechst Marion Roussel Inc.
P.O. Box 8480
Kansas City, MO 64114

The drug product is currently covered by Patent #4721619, expiring on January 26, 2005. There are no exclusivity provisions.

The firm originally filed Paragraph III Certification, 6/12/96. The application was amended to Paragraph IV Certification, 8/13/96. The firm submitted documentation of receipt of notice by the innovator, 8/15-16/96. No indication of response by the innovator has been filed in the application.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Diltiazem
Hydrochloride USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:
6/12/96 Original Submission.
8/13/96 Amendment - Paragraph IV Certification.
9/12/96 Amendment - Bioequivalence Telephone Amendment.
9/24/96 Amendment - Proof of Paragraph IV Notification Delivery.

FDA:
8/9/96 Receipt Acknowledged.
8/31/96 Issuance of Bioequivalence No Further Questions letter.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #19-471 - Hoechst Marion Roussel
DMF#
DMF

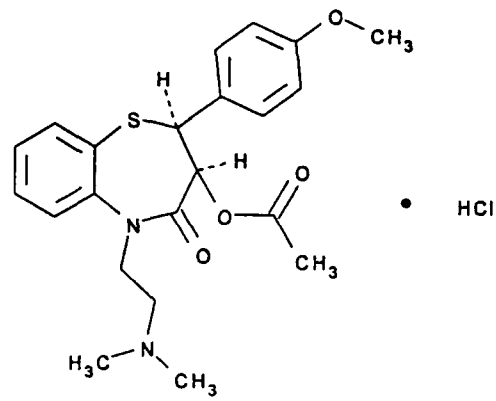
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
HG Capsule for oral administration

14. POTENCY
60 mg, 90 mg and 120 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
$C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.99



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation +98.3 ± 1.4° (c = 1.002 in methanol), 110° - 116° in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS
9/17/96 - Labeling review, C. Hoppes.
10/28/96 - Bioequivalence review, M. Park.

17. COMMENTS
Minor deficiencies were noted in the manufacturing and processing, and stability sections of the application.

Labeling was found to be unsatisfactory.

The Division of Bioequivalence found the drug product equivalent and granted waiver.

Acceptable EIR issued by the Office of Compliance.

Methods validation not required since drug substance and product are compendial.

The DMF for the drug substance was found satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application should be considered Not Approvable, Minor Amendment.

19. REVIEWER: Glen Jon Smith DATE COMPLETED: November 26, 1996

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pages of trade

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commercial

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant

AADA/ANDA: 74-910 APPLICANT: Mylan Pharmaceutical

DRUG PRODUCT: Diltiazem HCl Extended-Release Capsules, 60 mg, 90 mg, and 120 mg

A. Deficiencies:

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered to represent a MINOR AMENDMENT and should be so designated in your cover letter. If you

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-910

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
Cardizem® SR Capsules, 60 mg, 90 mg, 120 mg
Hoechst Marion Roussel Inc.
P.O. Box 8480
Kansas City, MO 64114

The drug product is currently covered by Patent #4721619, expiring on January 26, 2005. There are no exclusivity provisions.

The firm originally filed Paragraph III Certification, 6/12/96. The application was amended to Paragraph IV Certification, 8/13/96. The firm submitted documentation of receipt of notice by the innovator, 8/15-16/96. No indication of response by the innovator has been filed in the application.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Diltiazem
Hydrochloride USP

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

9. AMENDMENTS AND OTHER DATES:
Firm:

6/12/96	Original Submission.
8/13/96	Amendment - Paragraph IV Certification.
9/12/96	Amendment - Bioequivalence Telephone Amendment.
9/24/96	Amendment - Proof of Paragraph IV Notification Delivery.
11/11/96	Correspondence - Acknowledgement of Bioequivalence Letter of 8/31/96.
1/15/97	**Amendment - Response to Agency's letter of 12/27/96.**

FDA:

8/9/96	Receipt Acknowledged.
8/31/96	Issuance of Bioequivalence No Further Questions letter.
12/27/96	Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #19-471 - Hoechst Marion Roussel
DMF#
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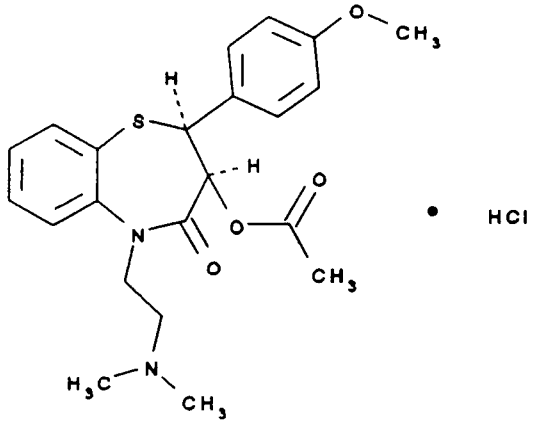
13. DOSAGE FORM
HG Capsule for oral administration

14. POTENCIES
60 mg, 90 mg, and 120 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
$C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.99



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation +98.3 ± 1.4° (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS
9/17/96 - Labeling review, C. Hoppes.
10/28/96 - Bioequivalence review, M. Park.
11/26/96 - Chemistry review #1, G.J. Smith.
2/21/97 - Labeling review, J. White.

17. COMMENTS

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

The Division of Bioequivalence found the drug product equivalent and granted waiver.

Acceptable EIR issued by the Office of Compliance.

Methods validation not required since drug substance and product are compendial.

The DMF for the drug substance was found satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application may be Approved.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: February 13, 1997

Redacted 14

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Chem Review #2

CDER Establishment Evaluation Report
for April 30, 1997

Application: **ANDA 74910/000**
Stamp: **13-JUN-1996** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265052730

Priority:
Org Code: **600**
Action Goal:
District Goal:
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXC (EXTENDED RELEASE CAPSUL**
Strength: **60 MG, 90 MG, 120 MG**

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 11-OCT-1996 by M. EGAS (HFD-324) 301-827-0062 OK

Establishment: **1110315**
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

DMF No:

Profile: **TTR** OAI Status: **NONE** ✓
Last Milestone: **OC RECOMMENDATI 11-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

Profile: **CSN** OAI Status: **NONE** ✓
Last Milestone: **OC RECOMMENDATI 25-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)*	DATE	PHONE NO.	EER ID #
☒ Original ☐ FollowUp ☐ FUR	June 18, 1996	594-0305	

REQUESTORS NAME: Tim Ames	DIVISION: Office of Generic Drugs	MAIL CODE: **HFD-647**

APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-910

BRAND NAME:	ESTABLISHED NAME: Diltiazem HCL Extended-Release Capsules, USP

DOSAGE STRENGTH: 60 mg, 90 mg, 120 mg	STERILE ☐Yes ☒ No

PROFILE CLASS: TTR	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*

APPLICANT'S NAME: Mylan Pharmaceuticals Inc.

APPLICANT'S ADDRESS: 781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504

COMMENTS :

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY	
	New Drug Substance Supplier				
2. Applicant	Drug Product manufacturing and testing				
3.					
4.					
5.					

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

cc: ANDA 74-910 HFD-647/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-647/JSimmons HFD-647/GJSmit