CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40326

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

NDA NUMBER: 40-326

FIRM: Mylan Pharmaceuticals, Inc

DOSAGE FORM: Tablet

STRENGTH: 0.5 mg, 1 mg and 2 mg

DRUG: Estradiol Tablets

CGMP STATEMENT/EIR UPDATED STATUS:
EER submitted for all the facilities listed in Section # 33 of CR # 2 is acceptable as of 10-14-98 by J. D. Ambrogio. See further comment in CR#2.

BIO STUDY:
Acceptable per bio review of 12/98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Container/closure system used for conducting stability studies are identical to those listed in container section.

LABELING:
Satisfactory per T. Watkins review completed on 3-29-99.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio batch is Lot # 25D004E for 2 mg strength tablets. Bio Waiver is requested for 0.5 mg and 1 mg tablets.

Source of NDS:
Estradiol Drug Substance:
Referenced DMF [ ] for [ ] is found adequate per review by Bing Cai dated 12-20-98.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Mylan's exhibit/stability batches are: lot # 25D002E for 0.5 mg tablets, lot # 25D005E for 1 mg tablet and lot # 25D002E for 2 mg

MSS 25D004E

tablets and their batch sizes are [ ] tablets. Three additional full scale batches were manufactured to support a change in scoring.

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

Mylan's intended production batch size for all three strengths are [ ] tablets .

Manufacturing process is identical to that used for the bio/stability batches.

cc: ANDA 40-326
Division File
Field Copy

Endorsements:

/S/ 4/7/99

HFD-625/M.Shaikh/3-30-99
HFD-625/M.Smela/3-30-99

/S/
4/7/99

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-326

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

4. LEGAL BASIS FOR SUBMISSION
The listed drug product is ESTRACE® by Bristol Myers Squibb approved in ANDA 81-295. Mylan certified that there are no patents that claim the listed drug referred to in this application per information available in current Edition of "Approved Drug Products with Therapeutic Equivalence Evaluations". Mylan further certified that the referenced product is not covered by any exclusivity provisions. The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Estradiol Tablets

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 8-13-98

FDA:
Accepted for filing: 8-14-98 (Acknowledgment letter issued on 9-3-98)

10. PHARMACOLOGICAL CATEGORY
Estrogen Therapy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 40-114...Watson Laboratories...approved ANDA
ANDA 81-295.. Bristol Myer Squibb
ANDA 40-275..ESI Lederle..Approved ANDA
DMF(

DMF
DMF

DMF
DMF
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DMF
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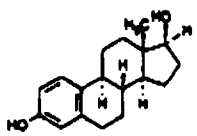
DMF
DMF
DMF

13. DOSAGE FORM
Tablets

14. POTENCY
0.5 mg, 1 mg and 2 mg

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: Estra-1,3,5(10)-triene-3-17-diol, (17β)

CAS NUMBER: [50-28-2]
MOLECULAR WEIGHT: 272.39
CHEMICAL FORMULA: $C_{18}H_{24}O_2$
STRUCTURE:



16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. GENERAL COMMENTS:

1. Components and composition statements is acceptable. Adequate information is submitted for the rationale of use and safety of each components. Composition for all the strength tablets are proportionate.
2. Adequate information is provided regarding facilities used for manufacturing/packaging/testing of the drug product.
3. Adequate information is submitted for manufacturing of the drug products.
4. Mylan's intended production size batch is (0.5 mg), tablets (1 mg) and Tablets (2 mg).
5. Mylan has submitted MV for all their method for active raw material, finished drug product.
6. Mylan exhibit batches are 25D002E (0.5 mg), 25D005E (1 mg) and

25D004E (2 mg) and their sizes are [redacted] tablets for all three strength tablets.

7. Mylan packaged the entire exhibit batches to meet OGD's current guideline regarding this.
8. Mylan manufactured all three strength tablets without scoring unlike the Listed drug product - Estrace.

B: COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments identified in section nos. 25, 28, 29, and 32 of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with facsimile amendment is being issued to the firm including all the deficiencies listed in this review.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 1-19-99

Redacted 24

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confidential

commercial

information

Chem #1

1. **CHEMISTRY REVIEW NO. 2**

2. ANDA # 40-326

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

4. LEGAL BASIS FOR SUBMISSION
Listed drug product is ESTRACE® by Bristol Myers Squibb approved in ANDA 81-295.

Mylan certified that there are no patents that claim the listed drug referred to in this application per information available in current Edition of "Approved Drug Products with Therapeutic Equivalence Evaluations".

Mylan also certified that the referenced product is not covered by any exclusivity provisions.

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Estradiol Tablets

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 8-13-98
- Facsimile Amendment: 3-10-99
- Bio Amendment: 3-10-99
- Telephone amendment: 3-23-99
- Telephone amendment: 3-25-99

FDA:
Accepted for filing: 8-14-98 (Acknowledgment letter issued on 9-3-98)
NA letter: 2-12-99

10. PHARMACOLOGICAL CATEGORY
Estrogen Therapy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 40-114...Watson Laboratories...approved ANDA
ANDA 81-295.. Bristol Myer Squibb
ANDA 40-275..ESI Lederle..Approved ANDA
DMF
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13. DOSAGE FORM
Tablets

14. POTENCY
0.5 mg, 1 mg and 2 mg

15. CHEMICAL NAME AND STRUCTURE
CHEMICAL NAME: Estra-1,3,5(10)-triene-3-17-diol, (17□)

CAS NUMBER: [50-28-2]
MOLECULAR WEIGHT: 272.39
CHEMICAL FORMULA: $C_{18}H_{24}O_2$
STRUCTURE: See CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS:
1. Mylan manufactured all three strength tablets with scoring like the listed drug product - Estrace.

2. Mylan's release and stability specifications became acceptable as they are identical to already approved ANDAs.

3. Referenced DMF remains adequate concurrent to this review. No new information is submitted.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 3-30-99

cc: ANDA 40-326
DUP File
Division File
Field Copy

Endorsements:

/S/ 4/7/99

HFD-625/M.Shaikh/3-30-99
HFD-625/M.Smela/3-30-99

/S/ 4/7/99

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Chem #2