CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-140

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. **CHEMISTRY REVIEW** No. 5

2. **ANDA # 75-140 (Terazosin Hydrochloride Capsules)**

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road, Morgantown, WV 26504-4310

4. **LEGAL BASIS FOR ANDA SUBMISSIONS** See CR #1 for details

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/A

7. **NONPROPRIETARY NAME** Terazosin Hydrochloride

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

9. **AMENDMENTS AND OTHER DATES**
* denotes the subject of this chemistry review

Mylan

06/06/97	ANDA submission (received at OGD 06/09/97)
07/25/97	Amendment (Re: patent issue)
09/03/97	Amendment (Re: bioequivalence issue)
01/30/98	Amendment (MINOR) (response to 11/12/97 MINOR-NA)
02/06/98	Amendment (addition of three new strengths)
02/06/98	New correspondence (Re: Patent)
02/12/98	Amendment (Re: submission of new table of contents)
02/24/98	Telephone amendment (Re: Bioequivalence)
03/03/98	New correspondence (from innovator, Re: Patent)
04/13/98	Amendment (Re: Patent issue)
07/15/98	Amendment (bioequivalence)
07/16/98	Amendment (FACSIMILE) (response to 06/19/98 fax- NA)
11/24/99	Amendment (MINOR): request for final approval
12/07/99	New correspondence (Re: Patent)
02/03/00	*Amendment (MINOR): response to NA (MINOR) letter

FDA:

07/07/97	Acknowledgment letter
10/23/97	Bio acceptance letter (for 5 mg strength)
11/12/97	NA (MINOR) (based on Chem Review #1, by S. Liu)
02/12/98	DOB called Mylan (no phone record in the jacket)
03/18/98	Bioequivalence letter
06/04/98	Bio letter (signed off on 03/18/98) faxed to Mylan
06/19/98	NA (FACSIMILE) (based on Chem Review #2, by S. Liu)
09/28/98	Tentative approval (based on Chem Review #3, by S.Liu)
02/02/00	NA (MINOR) (based on Chem Review #4, by S. Liu)

10. **PHARMACOLOGICAL CATEGORY** blood pressure regulator

11. **Rx or OTC** Rx

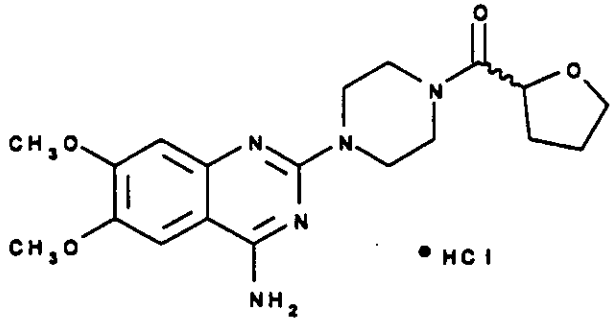
12. **RELATED IND/NDA**
HYTRIN® (Abbott): NDA #20-347 (approved 12/14/94)

13. **DOSAGE FORM** Capsules

14. **POTENCY** 1 mg, 2 mg, 5 mg, and 10 mg

15. **CHEMICAL NAME AND STRUCTURE**
Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolin-4-[(tetrahydro-2-furanyl)carbonyl]-,monohydrochloride,
MW = 423.89. Molecular formula $C_{19}H_{25}N_5O_4 \bullet HCl$

STRUCTURAL FORMULA:



16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**
Mylan submitted the minor amendment to respond to the CMC deficiencies cited in the NA (MINOR) letter of 02/02/00. Type II drug substance DMF was reviewed in connection with this minor amendment, and was found adequate.

EER was found acceptable 12/20/99.

There has been no change in the status of labeling and bioequivalnece.

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable

19. **REVIEWER** Shing H. Liu, Ph.D. **DATE COMPLETED** 02/10/2000

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Commercial/Confidential

Information and are not

releasable.

2/10/2000

Chemistry Review

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releasable.

2/2/00

Chemistry Comment

#38

JUN 19 1998

ANDA: 75-140 **APPLICANT:** Mylan Pharmacetical Inc.

DRUG PRODUCT: Terazosin Hydrochloride Anhydrous Capsules, 1 mg, 2 mg, 5 mg, and 10 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. For purposes of documentation, please re-submit certificates of analysis for all four strengths to include the current dissolution specifications recommended by the Division of Bioequivalence.

2. Please revise the specifications for dissolution for finished drug product release and stability to meet the specifications recommended by the Division of Bioequivalence.

3. The results of related compounds for lot #2C012N (5 mg strength) in the original COA (dated 05/16/97) are: individual, Total". Whereas in the revised COA (dated 01/20/98), the results for related compounds are "None Detected", even though the limit of quantitation remains in the method validation report dated 04/14/97 (p. 3236 of original ANDA submission) and 01/16/98 (p. 1105 and p. 1207 of the current amedment), respectively. Please comment.

4. In the revised certificate of analysis that you provided for your drug substance lot #6N115 (supplier's lot #1069D275), the melting range is This range appears to be too low for Terazosin Hydrochloride Anhydrous (please refer to melting point ranges reported in the Merck Index for Terazosin Hydrochloride).

   Furthermore, according to the U.S. Patent #5,504,207 that you included in your amendment dated April 13, 1998, the differential scanning thermogram trace of Terazosin Hydrochloride Anhydrous shows a sharp peak at (Figure 4 in the patent). In the same patent, the melting range for the dihydrate form was reported to be

   Please provide a copy of differential scanning thermogram trace for your lot #6N115. Also please comment on your melting point range result in terms of the reported melting range values for both dihydrate and anhydrous forms of Terazosin Hydrochloride.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. We require a satisfactory methods validation prior to approval of the ANDA. We will schedule the validation with the District Office once we receive the revised test method and specifications for dissolution.

2. We remind you that the dissolution specifications identified in the Agency's facsimile transmission dated June 4, 1998 need to be incorporated into your stability and quality control program for all four strengths (1 mg, 2 mg, 5 mg and 10 mg).

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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11/12/97

Chemistry Comments

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