CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75609

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-609

DRUG PRODUCT: Doxazosin Mesylate Tablets

FIRM: KV Pharmaceutical Company

DOSAGE FORM: Tablets **STRENGTH:** 1 mg, 2 mg, 4 mg, and 8 mg

CGMP: Statement/EIR Update Status:

The EER is acceptable (OC recommendation, 10/8/99).

BIO: The bioequivalence study was found acceptable by the Division of Bioequivalency, Office of Generic Drugs (7/13/00, Bio reviewer: Chandra S. Chaurasia).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The method validation for the drug substance and the drug product are satisfactory (3/3/00, FDA Denver district laboratory).

STABILITY: (Are containers used in study identical to those in container section?)
The containers used in the stability study are identical to those described in the container section.

LABELING:

Container, carton and insert labeling have been found satisfactory (Labeling approval summary 9/6/00, reviewed by Jim Barlow)

STERILIZATION VALIDATION (IF APPLICABLE):

Sterilization validation is not required.

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

Executed batch sizes:
tablets Doxazosin Mesylate Tablets, 1 mg
tablets Doxazosin Mesylate Tablets, 2 mg
tablets Doxazosin Mesylate Tablets, 4 mg
tablets Doxazosin Mesylate Tablets, 8 mg

DMF Doxazosin Mesylate drug substance was found to be adequate (6/24/99).

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

The exhibit batches were the stability batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

Proposed production batch sizes:
tablets of the Doxazosin Mesylate Tablets, 1 mg
tablets of the Doxazosin Mesylate Tablets, 2 mg
tablets of the Doxazosin Mesylate Tablets, 4 mg
tablets of the Doxazosin Mesylate Tablets, 8 mg

The manufacturing process will be the same as that was used for the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D. **DATE:** September 27, 2000
SUPERVISOR: Paul Schwartz, Ph.D. **DATE:** September 27, 2000

1. CHEMISTRY REVIEW NO. 1 (one)

2. ANDA # 75-609

3. NAME AND ADDRESS OF APPLICANT
KV Pharmaceutical Company
Attention: Hubert G Luther
2503 South Hanley Road,
St. Louis, MO 63144-2555

4. LEGAL BASIS FOR SUBMISSION
(1) The basis for KV Pharmaceutical Company's proposed ANDA for Doxazosin Mesylate Tablets, is approved, reference listed drug, Cardura®, the subject of NDA 19-668, held by Pfizer Inc. and containing 1 mg, 2 mg, 4 mg and 8 mg of doxazosin mesylate.
(2) Listing from "Approved Drug Products with Therapeutic Equivalence Evaluations" 18th Edition.
Paragraph III Certification
KV Pharmaceutical Company hereby certifies that, in his opinion and to the best of its knowledge, U.S. Patent No. 4,188,390 held by Pfizer Inc., will expire on October 18, 2000. This certification is made in accordance with Section 505 (j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94 (a)(12)(I)(A)(3).
Marketing Exclusive Statement
Cardura® is listed as having a marketing exclusivity for a new indication in the treatment of symptomatic benign prostatic hyperplasia. However, this exclusivity expired February 6, 1998. Therefore, to the best of our knowledge, this drug is not currently entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Doxazosin Mesylate Tablets

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

9. AMENDMENTS AND OTHER DATES:
Date of submission: March 26, 1999

10. PHARMACOLOGICAL CATEGORY
Antihypertension

11. Rx or OTC
RX

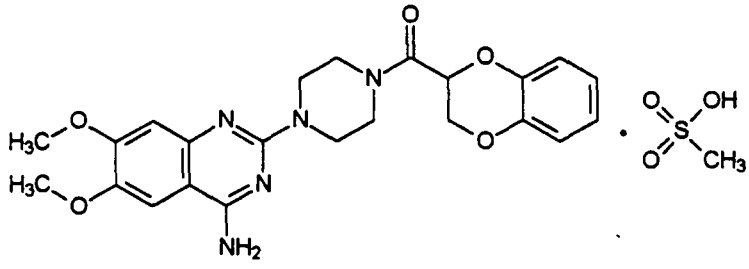
12. RELATED IND/NDA/DMF(s)
NDA 19-668, Cardura®, held by Pfizer Inc.
DMF doxazosin mesylate, held by

13. DOSAGE FORM
Tablets

14. POTENCY
1 mg, 2 mg, 4 mg, and 8 mg

15. CHEMICAL NAME AND STRUCTURE

Doxazosin Mesylate. Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate. $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$. 547.58. 77883-43-3. Antihypertensive.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable.

19. REVIEWER: Liang-Lii Huang, Ph.D.
DATE COMPLETED: October 6, 1999
Endorsed by Paul Schwartz, Ph.D./October 6, 1999

cc:

ANDA #75-609
ANDA DUP 75-609
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/Liang-Lii Huang, Ph.D./10/6/99. /S/ 10/13/99
HFD-627/ Paul Schwartz, Ph.D./ 10/6/99
HFD-617/Joseph Buccine/10/6/99

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Date: October 6, 1999

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Chem. Review #1

OCT 19 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-609 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. The specification of the melting range listed as "report" is not acceptable. Please specify the limit of melting range for the Doxazosin Mesylate drug substance.

2. Please provide the laboratory operating procedure entitled "melting range determination".

3. Please include the test and specification of the loss on drying for the Doxazosin Mesylate drug substance.

4. Please include the test and specifications of the organic volatile impurities for the Doxazosin Mesylate drug substance.

5. Please include the test and specification of particle size of the Doxazosin Mesylate drug substance.

6. Please include the limit of the total unknown impurities for the Doxazosin Mesylate drug substance.

7. Please include the identification test for for the Doxazosin Mesylate drug substance.

8. Please include the sample size for the test in your master production and control records. We recommend that the sample size of the material be not greater than three times the weight of an individual dose.

8. The master formulas of the subject product do not show any sampling instructions for test. Please provide the sampling plan (established SOP) of the final for the routine test.

9. In the proposed product specifications for Doxazosin Mesylate Tablets (p.3815), the analytical method should be specific. The updated version should be used, for example, method instead of method

10. In the dissolution testing, 900 mL 0.01N HCl, paddle, 50 rpm should be used. The specification of the Doxazosin Mesylate tablet dissolution should be NLT in 30 minutes. Please follow the method and procedures for

conducting the dissolution test of the Doxazosin Mesylate tablets recommended by the Division of Bioequivalence, Office of Generic Drugs (see attached).

11. Please include the testing in the master formulas as a process control test for the routine production of the Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg. We recommend that acceptance criteria for the be set as % (mean of individual results) with a RSD NMT %.

12. The in-process specifications on pages 3563, 3565, 3567 and 3569 should be incorporated into the master batch record for the routine production of the Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg.

13. Please include the resolution factor and the specification of the column efficiency in the system suitability test.

14. Please include information related to the manufacturer of the doxazosin mesylate drug substance in your stability report.

15. Specification for individual and total degradants/ impurities should be set for the product release and stability for all strengths.

16. Please include the identification test for mesylate counter ion for the Doxazosin Mesylate drug substance.

17. Based on the actual result obtained, please tighten the limit of the total impurities for the Doxazosin Mesylate drug substance.

18. Please include the specification of moisture content for the release of doxazosin mesylate tablets.

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

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

2. The FDA district office will be performing method validation on the drug substance and the finished drug product. Please submit samples promptly when so requested.

3. Bioequivalence of your product with the innovator product has not been established.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.

Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA #75-609
ANDA DUP 75-609
DIV FILE
Field Copy

1. CHEMISTRY REVIEW NO. 2 (two)

2. ANDA # 75-609

3. NAME AND ADDRESS OF APPLICANT
KV Pharmaceutical Company
Attention: Hubert G Luther
2503 South Hanley Road,
St. Louis, MO 63144-2555

4. LEGAL BASIS FOR SUBMISSION
(1) The basis for KV Pharmaceutical Company's proposed ANDA for Doxazosin Mesylate Tablets, is approved, reference listed drug, Cardura®, the subject of NDA 19-668, held by Pfizer Inc. and containing 1 mg, 2 mg, 4 mg and 8 mg of doxazosin mesylate.
(2) Listing from "Approved Drug Products with Therapeutic Equivalence Evaluations" 18th Edition.
Paragraph III Certification
KV Pharmaceutical Company hereby certifies that, in his opinion and to the best of its knowledge, U.S. Patent No. 4,188,390 held by Pfizer Inc., will expire on October 18, 2000. This certification is made in accordance with Section 505 (j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94 (a)(12)(I)(A)(3).
Marketing Exclusive Statement
Cardura® is listed as having a marketing exclusivity for a new indication in the treatment of symptomatic benign prostatic hyperplasia. However, this exclusivity expired February 6, 1998. Therefore, to the best of our knowledge, this drug is not currently entitled to a period of marketing exclusivity.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Doxazosin Mesylate Tablets

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

9. AMENDMENTS AND OTHER DATES:
Date of submission: March 26, 1999
Major amendment: February 7, 2000
Bioequivalency amendment: June 9, 2000

10. PHARMACOLOGICAL CATEGORY
Antihypertension

11. Rx or OTC
RX

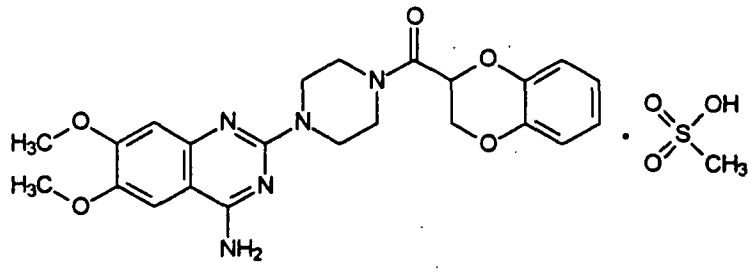
12. RELATED IND/NDA/DMF(s)
NDA 19-668, Cardura®, held by Pfizer Inc.
DMF doxazosin mesylate, held by

13. DOSAGE FORM
Tablets

14. POTENCY
1 mg, 2 mg, 4 mg, and 8 mg

15. CHEMICAL NAME AND STRUCTURE

Doxazosin Mesylate. Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate. $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$. 547.58. 77883-43-3. Antihypertensive.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable.

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. August 4, 2000
Endorsed by Paul Schwartz, Ph.D./August 4, 2000

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Chem. Review #2

1. CHEMISTRY REVIEW NO. 3 (three)

2. ANDA # 75-609

3. NAME AND ADDRESS OF APPLICANT
KV Pharmaceutical Company
Attention: Hubert G Luther
2503 South Hanley Road,
St. Louis, MO 63144-2555

4. LEGAL BASIS FOR SUBMISSION
satisfactory per review #2

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Doxazosin Mesylate Tablets

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

9. AMENDMENTS AND OTHER DATES:
Date of submission: March 26, 1999
Major amendment: February 7, 2000
Bioequivalency amendment: June 9, 2000
Fax amendment: August 21, 2000
Telephone amendment: September 12, 2000

10. PHARMACOLOGICAL CATEGORY
Antihypertension

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)
NDA 19-668, Cardura®, held by Pfizer Inc.
DMF doxazosin mesylate, held by

13. DOSAGE FORM

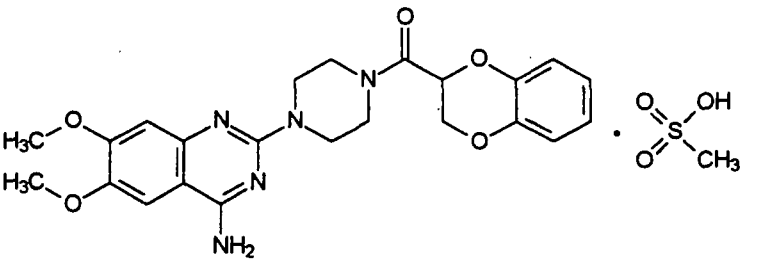
Tablets

14. POTENCY

1 mg, 2 mg, 4 mg, and 8 mg

15. CHEMICAL NAME AND STRUCTURE

Doxazosin Mesylate. Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, mono-methanesulfonate. $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$. 547.58. 77883-43-3. Antihypertensive.



16. RECORDS AND REPORTS
N/A.

17. COMMENTS
This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable.

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. September 25, 2000
Endorsed by Paul Schwartz, Ph.D./September 25, 2000

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Chem. Review #3

AUG 14 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-609 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Based on your results, the total impurities for the Doxazosin Mesylate drug substance should be further tightened.

2. We disagree with you that a specification for total impurities is unnecessary under the current conditions (page 9 of the major amendment dated 2/9/00). The individual and total impurities of the Doxazosin Mesylate Tablets should be tested and monitored at each scheduled stability station. Please include the test and specifications of individual unknown, total unknown, and total impurities for the product release and stability.

3. The FDA Denver district laboratory has completed the method validation on the drug substance and the finished drug product. Please respond to the following comments:

   (a) The equations for the % related compounds and dissolution tests for the finished product have a minor error. The equation shows the result taken times

   (b) The raw material method for related compounds utilizing the procedure was satisfactory except for the use of reference solution II. On the that the FDA Denver laboratory used, the spot was barely visible. You should switch from the procedure to the finished product related compounds procedure for better accuracy of the impurities, especially since the methodology is already available.

4. Your proposed specification of Q in 45 minutes is not acceptable. The following in vitro dissolution testing should be incorporated into your manufacturing controls and stability program:

   Apparatus: USP Apparatus II (paddle) at 50 rpm
   Medium: 900 mL of 0.01N Hydrochloride at 37°C
   Tolerance: NLT (Q) in 30 minutes.

Please provide stability data to demonstrate that your product meets these specifications.

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

Please submit available room temperature stability data.

Sincerely yours,

/S/ 9/8/00

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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75609/000**
Stamp: **30-MAR-1999** Regulatory Due:
Applicant: **KV PHARM**
2503 SOUTH HANLEY RD
SAINT LOUIS, MO 63144

Priority:
Org Code: **600**
Action Goal:
District Goal: **29-FEB-2000**
Brand Name:
Established Name: **DOXAZOSIN MESYLATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **1MG,2MG,4MG,AND 8MG**

FDA Contacts: **E. MCNEAL (HFD-170) 301-827-7410 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-APR-1999**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **1937079**
KV PHARMACEUTICAL CO
2303 SCHUETZ RD WESTPORT FACI
SAINT LOUIS, MO 63146
DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-APR-1999**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75609/000**
Stamp: **30-MAR-1999** Regulatory Due:
Applicant: **KV PHARM**
2503 SOUTH HANLEY RD
SAINT LOUIS, MO 63144

Priority: Org Code: **600**
Action Goal: District Goal: **29-FEB-2000**
Brand Name:
Established Name: **DOXAZOSIN MESYLATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **1MG,2MG,4MG,AND 8MG**

FDA Contacts: **E. MCNEAL (HFD-623) 301-827-5848 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 08-OCT-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 26-APR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-APR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **1937079**
KV PHARMACEUTICAL CO
2303 SCHUETZ RD WESTPORT FACII
SAINT LOUIS, MO 63146

DMF No:
AADA No:

Profile: **TCM** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-APR-1999**
Decision: **ACCEPTABLE**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**
