

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75609

ADMINISTRATIVE DOCUMENTS

**APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number: 75-609 Date of Submission: August 21, 2000 & August 23, 2000
 Applicant's Name: KV Pharmaceutical Company.
 Established Name: Doxazosin Mesylate Tablets, 1 mg, 2mg, 4 mg & 8 mg

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? **Yes**

CONTAINER Labels: Bottles of 100 and 1000 tablets-

Satisfactory in final print as of the August 21, 2000 submission

PROFESSIONAL PACKAGE INSERT Labeling:

Satisfactory in final print as of the August 23, 2000 submission

PATIENT PACKAGE INSERT-

Satisfactory in final print as of the August 21, 2000 submission

Revisions needed post-approval: **None**

BASIS OF APPROVAL:

Was this approval based upon a petition? **No**

What is the RLD on the 356(h) form: **Cardura®**

NDA Number: **19-668**

NDA Drug Name: **Cardura®**

NDA Firm: **Pfizer; N 19-668; Approved July 29 1997; Revised June 1997.**

Date of Approval of NDA Insert and supplement: **July 29, 1997; NDA 19-668/S-009**

Has this been verified by the MIS system for the NDA? **Yes**

Was this approval based upon an OGD labeling guidance? **No**

Basis of Approval for the Container Labels: **Most recently approved labels of the reference listed drug, approved November 2, 1990.**

OTHER COMMENTS: As of the August 21, 2000 submission, KV has withdrawn the unit-dose/carton of 100 tablets from the application. Therefore, no final printed carton/unit-dose labeling was submitted.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. 500 count bottle for this product		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility Information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T _{1/2} and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. INSERT/PATIENT PACKAGE INSERT:

Labeling review was based on the most recently approved labeling of Cardura® (Pfizer: Approved July 29, 1997; Revised 6/97).

Note that a labeling supplement (012) for NDA 19-668 was found *approvable* on April 26, 2000. At the time of this review, it is yet to be fully approved.

CONTAINER:

Labeling review based on Most recently approved container labels of Cardura®, approved November 2, 1990.

2. Storage/Dispensing recommendations:

USP: None

NDA: Store below 86°F(30°C)

ANDA: Store at controlled room temperature 15°C-30°C(59°F- 86°F).

We will not ask the firm to revise since this is a more stringent request.

3. In the opinion of the applicant and to the best of our knowledge, U.S. Patent No. 4188390 held by Pfizer inc. For Doxazosin Mesylate will expire on October 18, 2000. An exclusivity for the new indication of treating Benign prostatic hyperplasia expired on February 6, 1998. Therefore, the firm is filing a paragraph III and will NOT market their product until the expiration of the patent.
4. Components/Composition
The list of inactive ingredients in the DESCRIPTION section appears to be consistent with the firm's components and composition statement.[vol. B. 1.2, pg 2594, 2595, 2596 2597 & 2599]
5. Scoring
The reference listed drug scores 1 mg, 2mg 4 mg and 8 mg tablets.
The firm proposes the same configuration as the RLD.
6. Product Line:
The innovator markets their product in bottles of 100 and unit-dose packages of 100.
The applicant proposes to market their product in bottles of 100 & 1000 tablets.[see OTHER COMMENTS]
7. The tablet imprintings **have been** accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.(Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).See vol B. 1.4 pgs. 3818, 3821, 3824 & 3827.
8. Container/Closure:
All containers used are HDPE. The firm intends to market their product in bottles of 100 tablets with a CRC closure and bottles of 1000 tablets with a CRC closure system.
(See page 3578 in Vol. B. 1.4)

Date of Review: 8/30/00 Date of Submission: 8/21/00 & 8/23/00

Reviewer: Jim Barlow

Date:

Team Leader: John Grace

Date:

cc: ANDA: 75-609
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)

Review

data in the CRFs were reviewed by the study coordinator. Additionally, our investigation revealed no significant discrepancies between data in CRFs and the source data for Study

Conclusion:

We recommend that the clinical data for studies
be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.


Sriram Subramaniam, Ph.D.

cc:

HFD-45/Lepay

HFD-48/Fujiwara/Subramaniam(2)/cf

HFD-650/Sanchez/Fan/Chaurasia

HFR-SE1535/Frazier

Class: VAI - AAI Clinic, Durham, NC

Draft:SS

Edited:MKY MKY 6/8/00

File:5297;0:\BE\75609kvp.dox

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-609

Dates of Submission: February 9, 2000

Applicant's Name: KV Pharmaceutical Company

Established Name: Doxazosin Mesylate Tablets, 1 mg, 2mg, 4 mg & 8 mg

Labeling Deficiencies:

1. **CONTAINER** - bottles of 100 and 1000 tablets
Left Side Panel; revise the " *Each tablet contains..." statement to read as follows:

*Each tablet contains doxazosin mesylate equivalent to xx mg doxazosin. [lower case "doxazosin mesylate"]
2. **CARTON** - Unit-dose cartons of 100
Front Panel; revise the " *Each tablet contains..." statement to read as follows:

*Each tablet contains doxazosin mesylate equivalent to xx mg doxazosin. [make "tablet" singular and utilize lower case "doxazosin mesylate"]
3. **UNIT-DOSE BLISTERS**
Satisfactory in **draft** as of the February 9, 2000 submission
4. **INSERT**
 - a. **CLINICAL PHARMACOLOGY**

Table 1, Study 2 -

Revise to include an asterisk where indicated by the reference listed drug to be in accordance.
 - b. **PRECAUTIONS**

Drug Interactions; first paragraph, second sentence -

...indicate that doxazosin has...[spelling "doxazosin"]
5. **PATEINT PACKAGE INSERT**
Satisfactory in **draft** as of the March 26, 19999 submission

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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2
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Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP Item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. 500 count bottle for this product		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringes, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
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Labeling(continued)	Yes	No	N.A.
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ANDA: Store at controlled room temperature 15°-30°C(59°-86°F).

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The applicant proposes to market their product in bottles of 100, 1000 and unit-dose packages of 100 tablets.
7. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See vol B. 1.4 pgs. 3818, 3821, 3824 & 3827.
8. **Container/Closure:**
All containers used are HDPE. The firm intends to market their product in bottles of 100 tablets with a CRC closure and bottles of 1000 tablets with a CRC closure system.
(See page 3578 in Vol. B. 1.4)

Date of Review: 2/17/00

Date of Submission: 2/9/00

Primary Reviewer: Jim Barlow

Date: 5/18/00

Team Leader: John Grace

Date:

cc:
ANDA: 75-609
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)

Review

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-609

Date of Submission: March 26, 1999

Applicant's Name: KV Pharmaceutical Company

Established Name: Doxazosin Mesylate Tablets, 1,mg, 2 mg, 4 mg & 8 mg.

Labeling Deficiencies:

1. CONTAINER - bottles of 100 and 1000 tablets.
 - i. Front Panel: Revise to read -[add an asterisk]

**Doxazosin Mesylate
Tablets**

X mg*

- ii. Left Side Panel: Revise to read as follows -

*Each tablet contains doxazosin mesylate equivalent to xx mg doxazosin.
 - iii. Please assure that the established name and expression of strength are the most prominent print on the label.
 - iv. Front Panel: Please clarify what "ETHEX" represents. If it is a manufacturer, packager or distributor, it must be labeled to be in accordance with CFR 201.1(h)(5). Please revise and/or comment.

2. CARTON - Unit-dose cartons of 100

- i. Front Panel and Side Panels - Revise to read -[add an asterisk]

**Doxazosin Mesylate
Tablets**

X mg*

ii. Front panel - revise to read as follows -

*Each tablet contains Doxazosin Mesylate equivalent to xx mg Doxazosin.

iii. See comment 1.(iv.) listed above.

3. UNIT-DOSE BLISTER LABELS

Revise to read as follows -

Doxazosin Mesylate Tablets

X mg*

4. INSERT

a. DESCRIPTION

i. First paragraph, third sentence - revise to read as follows:

The molecular formula for doxazosin.. [replace with "molecular"]

ii. Second paragraph, second sentence - revise to read as follows:

Each doxazosin mesylate tablet (colored), for oral administration, contains ...

iii. Third paragraph, first sentence - revise to read as follows:

In addition, each doxazosin mesylate tablet contains the following inactive ingredients: lactose...,

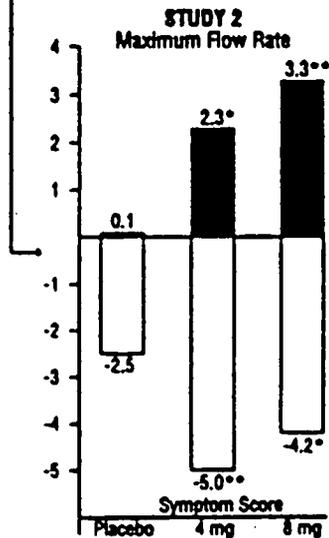
b. CLINICAL PHARMACOLOGY

i. Table 1 - Study 1 & Study 2: Revise to read "Doxazosin mesylate" throughout the text.

ii. Table 1 - Study 2: Revise as follows:

TABLE 1
SUMMARY OF EFFECTIVENESS DATA IN PLACEBO-CONTROLLED TRIALS

	SYMPTOM SCORE ^a			MAXIMUM FLOW RATE (mL/sec)		
	N	MEAN BASELINE	MEAN ^b CHANGE	N	MEAN BASELINE	MEAN ^b CHANGE
STUDY 1 (Titration to maximum dose of 8 mg)^c						
Placebo	47	15.6	-2.3	41	9.7	+0.7
doxazosin mesylate	49	14.5	-4.9**	41	9.6	+2.9**
STUDY 2 (Titration to fixed dose-14 weeks)^d						
Placebo	37	20.7	-2.5	30	10.6	+0.1
doxazosin mesylate 4mg	38	21.2	-5.0**	32	9.8	+2.3*
doxazosin mesylate 8mg	42	19.9	-4.2*	36	10.5	+3.3**
STUDY 3 (Titration to fixed dose-12 weeks)						
Placebo	47	14.9	-4.7	44	9.9	+2.1
doxazosin mesylate 4mg	46	16.6	-6.1*	46	9.6	+2.6



- ^a ALJA questionnaire (range 0-30) in studies 1 and 3. Modified Boyersky Questionnaire (range 7-39) in study 2.
- ^b Change is to endpoint.
- ^c Change is to fixed-dose efficacy phase, 22-26 hours post-dose for studies 1 and 3 and 2-6 hours post-dose for study 2.
- ^d Study in hypertensives with BPH
- * 36 patients received a dose of 8 mg doxazosin mesylate
- * (**) p < 0.05 (0.01) compared to placebo mean change.

iii. Replace "doxazosin mesylate" with "doxazosin" throughout the text except when referring to a specific dose.

c. INDICATIONS AND USAGE

i. Benign Prostatic Hyperplasia (BPH) - First sentence - Revise to read as follows:

Doxazosin mesylate tablets are indicated...

ii. Hypertension - First sentence - revise to read:

Doxazosin mesylate tablets are also indicated...

d. CONTRAINDICATIONS

Doxazosin mesylate tablets are contraindicated...

e. PRECAUTIONS

Pediatric Use - revise to read:

...have not been established in pediatric patients.

f. DOSAGE AND ADMINISTRATION

Replace _____ with "doxazosin mesylate tablet" throughout the text.

g. HOW SUPPLIED

i. Second paragraph -

Please revise your tablet descriptions throughout this section to be the same as your tablet descriptions found in your Controls for Finished Dosage form section. (to read as follows)

Doxazosin mesylate tablets are available as:

1 mg, gray, capsule-shaped tablets, debossed "ETH266" on one side and, "1", bisect, "mg", on the other side.

2 mg, yellow,...

ii. We encourage you to relocate the "Rx only" statement to the Title section of the package insert.

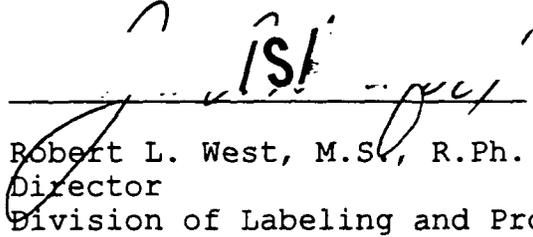
5. PATIENT PACKAGE INSERT

Satisfactory in **draft** as of March 26, 1999 submission.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION/MEETING

Reference is made to the firm fax dated 10/22/99 (attached). After consulting with Liang Lii Huang, we provided the firm a response to their questions. Please refer to the notes in the margins of the fax.

cc:
ANDA 75-609
T-con Binder

DATE: 10/27/99

ANDA NUMBER:
75-609

IND NUMBER:

TELECON:

INITIATED BY FDA:

PRODUCT NAME:
Doxazosin

FIRM NAME:
KV Pharmaceuticals

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD:
Herb Luther for
Angel Rodriguez

TELEPHONE NUMBER:
(314)645-6600

SIGNATURE:
Joe Buccine

