CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74404

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 74-404

Date of Submission: June 16, 1996

Applicant's Name: Martec Pharmaceutical, Inc.

Established Name: Atenolol and Chlorthalidone Tablets USP, 50 mg/25 mg and 100 mg/25 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

   Please note that this drug product has become the subject of a USP monograph in the fourth supplement to USP 23. We encourage the inclusion of USP in the established name of this product on all labels and labeling.

2. INSERT

   a. See GENERAL comment.

   b. DESCRIPTION

      i. We encourage the inclusion of the molecular weights of atenolol and chlorthalidone in this section. Please refer to USP 23 and the fourth supplement to USP 23 for guidance.

      ii. Make the following revision in the line following the structural formula of chlorthalidone, "...12/mg...", ("g" rather than "q").

      iii. Indicate the route of administration for your product, e.g., "Each atenolol and chlorthalidone...for oral administration contains...", (two places). We refer you to 21 CFR 201.57(a)(ii) for guidance.

c. **WARNINGS**

i. Ischemic Heart Disease

Revise the last sentence to read, "...only for hypertension.".

ii. Concomitant Use of Calcium Channel Blockers

Revise this subsection to read:

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible (See PRECAUTIONS).

iii. Pregnancy and Fetal Injury

Revise the second sentence to read:

Atenolol crosses the placental barrier and appears in cord blood.

d. **PRECAUTIONS**

i. Drug Interactions

Make the following revision in the second sentence, "...e.g., reserpine...", (comma rather than period following "e.g.").

ii. Animal Toxicology

Make the following revision in the first sentence, "...month oral administration...".

iii. Use in Pregnancy

Revise this subsection heading as follows: Pregnancy: Teratogenic Effects, *Pregnancy Category D:*

e. DOSAGE AND ADMINISTRATION

Revise the first sentence as follows, "...(SEE INDICATIONS AND USAGE)...".

f. HOW SUPPLIED

i. See GENERAL comment.

ii. Make the following revision in the second line, "...round, bisected...", add a space.

Please prepare and submit final printed package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further 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.

/s/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: **74-404** Date of Submission: **July 18, 1997**

Applicant's Name: **Martec Pharmaceutical, Inc.**

Established Name: **Atenolol and Chlorthalidone Tablets USP, 50 mg/25 mg and 100 mg/25 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. In absence of a decision to reformulate this product, as discussed above, and in the interim period of your petition to the U.S.P. and subsequent adoption of your proposed dissolution specification by the U.S.P., the labels of your product must state the difference when an article differs from the standards of strength, quality, and purity as set forth in the Pharmacopeia. Thus, please revise your immediate container labels and package insert labeling as follows:

      Delete "U.S.P." from the established name and include an asterisk immediately afterwards as follows:

      Atenolol and Chlorthalidone Tablets*

      ____ mg / ____ mg

      *Product does not meet U.S.P. requirements for dissolution.

   Note: The asterisked statement about the product not meeting U.S.P. dissolution requirements must appear on the main panel of the container label and immediately beneath the established name in the package insert.

   b. As a result of the FDA Modernization Act of 1997 please make the following revision throughout your labels and labeling:

Replace the "CAUTION: Federal law..." statement with the symbol "℞ only".

2. INSERT

a. GENERAL

Increase prominence of superscripts, subscripts and numbers throughout the text.

b. DESCRIPTION

i. Each atenolol (lower case "a").

ii. Revise the structural formula of chlorthalidone to delete the lines protruding from the benzene group on the left. This could be misconstrued as methyl groups.

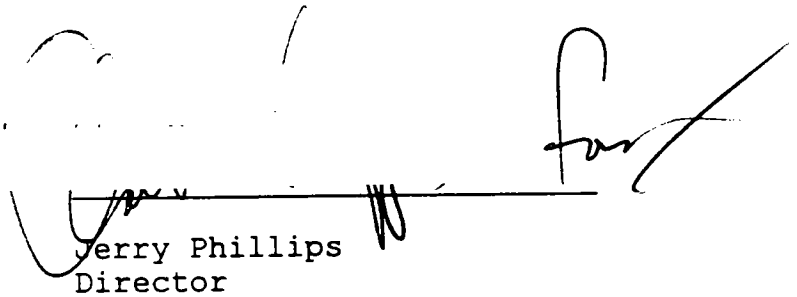
c. PRECAUTIONS

Delete "**Use in Pregnancy**" from subsection heading.

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

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.



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA APPROVAL SUMMARY

ANDA: 74-404

DRUG PRODUCT: Atenolol and Chlorthalidone Tablets USP, 50 mg/25 mg and 100 mg/25 mg

FIRM: Martec Pharmaceuticals, Inc.

DOSAGE FORM: Tablets

STRENGTHS: 50 mg/25 mg and 100 mg/25 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

3. Packaging, Labeling and Packaged Product Testing:

Martec Pharmaceutical, Ltd.
1800 N. Topping
Kansas City, Missouri 64120

4. Stability testing;

b. Finished Drug Product Packaged in Commercial Containers:

Martec Pharmaceutical, Ltd.
1800 N. Topping
Kansas City, Missouri 64120

4-20-98

(OK on 1-23-97 and ~~Pending~~ again).

anufacturer-Active Ingredients:

The manufacturers of the drug substance Atenolol and Chlorthalidone are listed as follows:

The manufacturer of the drug substance atenolol is:

Chlorthalidone

(OK on 1-23-97, and ~~pendin~~g again).

ontract Laboratories:

IO STUDY:

Satisfactory reviewed per Sikta Pradhan on 10-21-97.

100 mg/25 mg Tablets and 50 mg/25 mg Tablets, Lots# #0599A1 and #0596B1.

Bio provides acceptable letter dated October 21, 1997 with the following recommendation:
As the test product does not meet the current USP dissolution specification, you should submit a petition to the USP for modification of the current monograph for this product.

Firm intend to meet the compendial monograph by submitting a petition to the USP immediately after the FDA approval is granted requesting revision of the current USP monograph to include their dissolution method on 4-6-98 amendment.

Firm states in container Labeling "Product does not meet USP requirements for dissolution" on 4-6-98 amendment.

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

The proposed production batch (blank batch):

CHEMIST: Lucia C. Tang DATE: 4-14-98

SUPERVISOR: Ubrani Venkataram DATE: 4-24-98

74404AAP.P/Tang/4-14-98
F/T by pah/4/28/98
x:\new\firmsam\martec\ltrs&rev\74404.apf

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74404

CORRESPONDENCE

MINOR AMENDMENT

FEB 1 8 1997

ANDA/AADA: 74-404

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT Monteg Pharm. PHONE 816-241-4144
ATTN: Paul Sudhakar FAX 816-483-5432

FROM: Tim Ames PROJECT MANAGER (301-594-0309)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/ antibiotic application dated 9/3/93, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Atenolol and Chlorthalidone Tablets USP 50mg/25mg and 100mg/25mg

Reference is also made to your amendment(s) dated 1/16/96.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactiveated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. For further clarification or assistance please contact the Project Manager listed above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

Labels + labeling satisfactory for approval (see telecon thoy)
labeling rewardrafted 4/8/98 a Vezza

Telephone Amendment to ANDA 74-404

April 06, 1998.

Mr. Doug Sporn
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 286
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A

Should be AM not AF for Minor Amendment.

Attn: Mr. Adolph Vezza, Labeling Division, OGD.

RE: TELEPHONE Amendment to ANDA 74-404 for Atenolol and Chlorthalidone Tablets, 50 mg/ 25 mg and 100 mg/ 25 mg.

Dear Mr. Sporn:

Pursuant to a telephone communication of April 3, 1998 by Mr. Adolph Vezza, Martec Pharmaceutical, INC., herewith submits a **TELEPHONE** amendment to the above-mentioned ANDA.

Mr. Adolph Vezza indicated that the colored (maroon) front panel of container label for the 100 mg/25 mg product in the 100 count bottle was darker than the other labels resulting in poor legibility of the text which is in black. The container label has been revised to match the other package sizes and/also to improve the legibility of the text in the colored front panel.

12 copies of the final printed label and a side-by-side comparison with the label that was submitted in the March 19th amendment is provided in this amendment. Two copies of the entire amendment are provided for archival and review purpose.

Please contact me at (816) 241-4144 or at 800-822-6782, if additional information is required.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
Executive Vice President.

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Enclosures:
1. **: 12 copies of the revised container label for 100 mg/25 mg in 100 count bottle.**
2. **: 1 copy of side-by-side comparison.**

816 241-4144 CORPORATE OFFICE
800 822-6782 SALES & MARKETING
800 287-7576 FAX MACHINE

MAR 02 1998

38. Chemistry Comments to be Provided to the Applicant

AADA/ANDA: 74-404 APPLICANT: Martec Pharmaceuticals, Inc.

DRUG PRODUCT: Atenolol and Chlorthalidone Tablets USP, 50 mg/25 mg and 100 mg/25 mg

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies

The following comments address the issue of setting a dissolution specification, for your Atenolol and Chlorthalidone Tablets different from that found in United States Pharmacopeia 23.

On evaluation of your abbreviated application and review of formulation data, various dissolution profiles, and your discussion of the specific effects of your chosen formulation, we agree that the components of this formulation affect solubility to such an extent that current USP dissolution requirements cannot be met. We also note that your biequivalence study demonstrates your product and the reference listed drug to be equivalent.

The USP proposal and implementation of these requirements were after submission of your application. However, the Office position is that products described in a USP monograph are in fact official articles under the law, and should comply fully with the provisions of that monograph. In general, this could be accomplished through either reformulation of your product, or through a petition by you to the USP to change the current monograph dissolution specifications. Reformulation, depending on its extent, might require additional bioequivalence determination. Please advise how you intend to meet the compendial monograph requirements.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

MAR 02 1998

ANDA 74-404

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Martec Pharmaceuticals, Inc. PHONE: 816-241-4144

ATTN: Paul T. Sudhakar FAX: 816-483-5432

FROM: Timothy Ames PROJECT MANAGER (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated September 3, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atenolol and Chlorthalidone Tablets USP, 50 mg/25 mg and 100 mg/25 mg.

Reference is also made to your amendment(s) dated July 18, 1997, November 11, and December 8, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

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MARTEC
PHARMACEUTICAL, INC.

1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

AM noted
① To Chemistry Review
for Review then ② To
labeling reviewer
for review
7/24/97

Amendment to ANDA 74-404

July 18, 1997

Mr. Doug Sporn
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 278
7500 Standish Place
Rockville, MD 20855-2773

RE: MINOR Amendment to ANDA 74-404 for Atenolol/Chlorthalidone Tablets USP, 50 mg/25 mg, and 100 mg/25 mg.

Dear Mr. Sporn:

In response to the minor deficiency letter of February 18, 1997 from, OGD, and in accordance with 21 CFR 314.96, Martec Pharmaceutical, Inc. herewith submits an amendment to the above-mentioned ANDA.

All comments of the OGD, of letter of February 18, 1997 (presented as ***Attachment 1***) are addressed in this amendment.

Please contact me at (816) 241-4144 or at 1-800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar
Executive Vice President
Martec Pharmaceutical, Inc.

1. Response
2. Enclosures
   Attachment 1 – MINOR deficiency letter of February 18, 1997 .
   Attachments 2. to 8 – Response to various comments

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(816) 241-4144 CORPORATE OFFICE
(800) 822-6782 SALES & MARKETING
(816) 483-5432 FAX MACHINE

ANDA 74-404, ATENOLOL AND CHLORTHALIDONE TABLETS USP, 50 mg/25 mg AND 100 mg/25 mg.

RESPONSE TO MINOR DEFICIENCY LETTER OF FEBRUARY 18, 1997

I. Chemistry deficiencies

1. **DEFICIENCY**: The drug substance (Atenolol) and the drug product are now USP articles in USP 23 supplement 4. Please revise and resubmit tests and specifications accordingly.

RESPONSE: a. The drug substance ıas been contacted and the methods will be revised accordingly. Please see a letter of commitment provided by the supplier presented as ***Attachment 2***.

b. The method of analysis for the drug substance (Atenolol) a' the manufacturer of the drug product is provided as ***Attachment 3.***

c. The method of analysis for the drug product (Atenolol and Chlorthalidone) has been revised according to USP 23 supplement 4 and is provided as ***Attachment 4.*** The only difference is in the dissolution method, which consists of 500 mL of 0.1 N HCl instead of 500 mL of water. The discussion and justification for use of this dissolution media has been provided to Division of Bioequivalence in our letter of March 24, 1997.

The USP method of analysis will be used for finished product release testing only, whereas the validated stability indicating method provided in the ANDA will be used for ongoing and future stability testing of the drug product.

2. **DEFICIENCY**: Please note that compendial methods are regulatory and will be used in case of disputes.

RESPONSE: The comment is noted and is acceptable.

3. **DEFICIENCY:** Please clarify if the specification for ın related substances of Chlorthalidone (See Attachment 3i of June 16, 1996 Amendment) is fo'

RESPONSE : The ıs provided for ıith a limit of less than or equal ' Copies of the revised COAs are provided as ***Attachment 5.***

4. **DEFICIENCY**: Please do not respond to this letter until you have resolved all relevant issues with our Division of Bioequivalence.

RESPONSE: A fax was sent to Mr. Tim Ames requesting clarification of this issue (copy enclosed as ***Attachment 6***). In a telephone response on July 17, 1997, Mr. Ames. provided clarification that we should file the amendment immediately and that the Division of Bioequivalence has completed its review and has no significant comment.

II. Labeling deficiencies:

1. **General comment**:

   Response: Per your suggestion, **USP** has been included in the established name and the revised final container labels (12 copies) are provided as ***Attachment 7***.

   A side-by-side comparison of the proposed labeling with the last submission is provided as ***Attachment 7a.*** Differences are annotated.

2. **Insert**:

   The package insert has been revised according to the comments of your letter of February 18, 1997. (See ***Attachment 1***). 12copies of the final printed package insert is provided for your review as ***Attachment 8***

   A side-by-side comparison of the proposed package insert with the last submission is provided as ***Attachment 8a***. . Differences are highlighted.

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

Labeling Review
Completed 9/12/96

ANDA 74-404

June 16, 1996.

Mr. Douglas Sporn
Director
Division of Generic Drugs
HFD-600, Room 280
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rockville, MD 20855

JUN 19 1995

ORIG AMENDME

RE: MAJOR Amendment to ANDA 74-404
for Atenolol and Chlorthalidone Tablets, 50 mg/ 25 mg and 100 mg/25 mg

Dear Mr. Sporn:

In accordance with 21 CFR 314.20 and your letter of September 13, 1995, we are submitting an amendment to the above referenced ANDA. Reference is made to the not approvable letter from Division of Chemistry II of September 13, 1995.

All comments in your letter of September 13, 1995 are addressed in this amendment (submitted in 1 volume) in the same order as they appear in the letter.

If you should have any questions, please do not hesitate to contact me.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
Senior Vice President of Scientific Affairs

enclosures: 2 copies of 1 volume each.

(816) 241-4144 CORPORATE OFFICE
(800) 822-6782 SALES & MARKETING
(816) 483-5432 FAX MACHINE

Containers / labels satisfied in FPL / 100's & 1000's. See ~~letter~~ review re: package insert revision requests. 7/24/95

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

April 3, 1995

Dr. Douglas Sporn
Director
Division of Generic Drugs
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

N/MC
AMENDMENT

RE: **MAJOR Amendment to ANDA 74-404**
for Atenolol/Chlorthalidone Tablets 50 mg\25 mg and 100 mg\25 mg.

Dear Dr. Sporn:

In accordance with 21 CFR 314.120, we are submitting an amendment to the above referenced ANDA. Reference is made to the not approvable letter from Division of Chemistry II of March 11, 1994.

All the comments in your letter of March 11, 1994 are addressed in this amendment (submitted in 3 volumes) in the same order as they appear in the letter.

If you should have any questions, please do not hesitate to contact me.

Sincerely

Paul T. Sudhakar

Paul T. Sudhakar
Senior Vice President Scientific Affairs

Enclosures (3 volumes)

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APR 11 1995
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Nadene 4.24.95

(816) 241-4144 CORPORATE OFFICE
(800) 822-6782 SALES & MARKETING
(816) 483-5432 FAX MACHINE

ANDA 74-404

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping
P.O. Box 33510
Kansas City, MO 64120-3510

NOV 2 3 1993

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG: Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

DATE OF APPLICATION: September 3, 1993

DATE OF RECEIPT: September 10, 1993

DATE OF ACCEPTABLE FILING: November 9, 1993

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

11/23/93

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA#74-404
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-632/MBennett

-3/93

Endorsements:
HFD-632/Gordon Johnston/WRickmar 11/19/93
HFD-632/WRussell WR 11/19/93
HFD-637/JSimmons/ 11/21/93
Russell\74-404 v
F/T by bcw/11-19-93
ANDA Acknowledgement Letter!

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

505 (j)(2)(A) info acceptable for filing WP 11/15/93

Paul 11/17/93

November 08, 1993

Mr. Robert W. Pollock
Director
Division of Labeling
and program Support
Office of Generics
Center for Drug Evaluation and Research
5600 Fishers lane
Food and Drug Administration
Rockville, MD 20857

NDA ORIG AMENDMENT

RE: ANDA 74-404, Atenolol/Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

Dear Mr. Pollock:

This is in response to your Refusal to File letter of October 20, 1993, for ANDA 74-404, Atenolol/Chlorthalidone Tablets 50 mg/25 mg and 100 mg/25 mg.

The response to each of your reasons for refusing to file is addressed in the order in which they are listed in your letter.

Four sets of the entire response are provided, two sets for the chemistry and manufacturing section(review copy and archival copy) and two sets for the pharmacokinetics section (review copy and archival copy).

Please contact me if you if you need additional information.

Sincerely,

Paul T. Sudhakar
V.P. Regulatory Affairs

enclosures

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ORIGINAL

816 241-4144 CORPORATE OFFICE
800 822-6782 SALES & MARKETING
816 483-5432 FAX MACHINE

Fax To Dr. Hasselquist

October 29, 1998

Re: Roy V. Castle, Jr.

I have been taking the pergolide at .1mg at bedtime and have received some relief from the leg movements, but they are still fairly significant sometimes. Should I keep taking the 1mg at bedtime dose or increase to .2mg at bedtime for 14 days to see if that eliminates the problem?

I can be reached at 301-827-3455 during the day or home 301-972-2394. The pharmacy number is 301-414-1411 to call in a new prescription.

Thanks

Roy V. Castle, Jr.

ANDA 74-404

OCT 20 1993

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

Dear Sir:

Reference is made to your abbreviated new drug application (ANDA) submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

We have given your ANDA a preliminary review, and we find that it is not sufficiently complete to merit substantive review. Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

We are refusing to file this ANDA under 21 CFR 314.101(d) for the following reasons:

2. Failure to provide a side-by-side comparison of the proposed container labels with the approved container labels of the reference listed drug with all differences annotated and explained [314.94(a)(9)(iv)]. Labeling as defined in the regulations includes container labels and the package insert labeling.

3. Failure to provide English translations of the Certificate of Analysis for Atenolol presented on pages 210, 211 and 212 of the application.

In addition please provide the complete street address of the manufacturing facility utilized in the production of the active ingredient chlorthalidone and the complete street address o

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized in 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell, R.Ph.
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

10/19/93

Robert W. Pollock
Director
Division of Labeling
and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-404
DUP/Division File
HFC-130/JAllen
HFD-320/
HFD-650/
HFD-637/JSimmons
HFD-600/Reading File
R/D initialed by GJohnston
bcw/9-27-93/74-404
F/T by bcw/9-27-93
refuse to file

10/14/93 10/18/93 10/19/93 10/19/93

D/U

ANDA 74-404

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

SEP 13 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated September 3, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act for Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

Reference is also made to your amendment dated April 3, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

2. Your revised dissolution specifications remains not acceptable to our Division of Bioequivalence.

The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test drug should meet the following specifications:

> Not less than of the labeled amount of atenolol and of chlorthalidone in the tablet is dissolved in 30 minutes and 60 minutes, respectively.

Please submit the revised certificates of analysis for the finished product and the stability protocol and stability data based on the above comments.

3. Please completely describe the scoring configuration and markings on the tablets (e.g., which faces are scored and/or marked) both in your batch release and labeling records.

4.

5.

6. The method validation of Atenolol/Chlorthalidone Tablets 50 mg/25 mg and 100 mg/25 mg can not be conducted until the specifications for in vitro dissolution testing are found satisfactory. Please submit the revised analytical methodology regarding in vitro dissolution testing, consistent with Division of Bioequivalence recommendation, for the drug product.

7. The proposed five years expiration date for the bulk package is not acceptable. We would consider 6-month expiration dating for the bulk containers. 6-month expiration dating should be from the date of manufacture. Please submit a revised stability protocol reflecting a shorter expiration date, for the bulk package supported by data.

B. Labeling Deficiencies

Container (100's and 1000's):

Satisfactory.

Insert:

1. Title - Revise the third line to read:

50 mg/25 mg and 100 mg/25 mg.

2. DESCRIPTION

a. Second sentence - "...agent (atenolol)...", (close parenthesis).

b. Third and fifth paragraph - "...°C...", rather than "...C°...".

c. We encourage you to alphabetize your inactive ingredients.

d. Penultimate paragraph -
Each atenolol and chlorthalidone 50 mg/25 mg tablet contains:
Each atenolol and chlorthalidone 100 mg/25 mg tablet contains:

3. INDICATIONS AND USAGE

Atenolol and Chlorthalidone Tablets are...

4. WARNINGS

a. In the fourth paragraph, let the sentence, "In patients with impaired hepatic function...", begin a new paragraph.

b. Immediately following the subsection **"Ischemic Heart Disease"**, add the following subsection:

Concomitant Use of Calcium Channel Blockers: When calcium channel blockers are coadministered with beta blockers, bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See PRECAUTIONS).

c. Anesthesia and Major Surgery (first paragraph)

...in the majority...(1 to 2 mg IV).

d. In the last sentence of the first paragraph of the subsection **"Metabolic and Endocrine Effects"**, make the following revision, "...beta blockers

does not...", (spelling "does").

e. Revise the first paragraph of the "Pregnancy and Fetal Injury" subsection as follows:

Pregnancy and Fetal Injury: Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol and thiazides cross the placental barrier and appear in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5. PRECAUTIONS

a. Add the following text as the second paragraph in the "Drug Interactions" subsection:

Calcium channel blockers may also have an additive effect when given with atenolol and chlorthalidone. (see WARNINGS).

b. Carcinogenesis, Mutagenesis, Impairment of Fertility:

i) Second sentence, "...in increased incidences...".

ii) Second sentence, "...*in vivo* cytogenetics test (Chinese...", (italicize "*in vivo*" and capital "C" in "Chinese").

c. Nursing Mothers:

i) First sentence, "...a ratio...in plasma.".

ii) Last sentence, "...develop adverse...".

d. Pediatric Use:

...in pediatric patients...

6. ADVERSE REACTIONS

a. Revise the first sentence of the first paragraph immediately following the table as follows:

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia and visual disturbances.

b. **Potential Adverse Effects:**

i) (Nervous System): Delete "hallucinations" and "visual disturbances".

ii) (Miscellaneous):

1) Second sentence, "...most cases,...", (comma).

2) Revise the last sentence of the first paragraph to read:

...therapy. (See DOSAGE AND ADMINISTRATION).

7. OVERDOSAGE

a. **Atenolol:**

Bold the subsection heading and make the following revision in the last sentence of the second paragraph, "...the physician's...".

b. BRADYCARDIA:

Glucagon in a...

c. ELECTROLYTE DISTURBANCE:

Allow the sentence, "Based on the...", to begin a new paragraph.

d. **Chlorthalidone:**

Bold the subsection heading as above.

8. HOW SUPPLIED

Second paragraph, "...and 451 and is...", (add a space).

Revise your package insert labeling, then prepare and submit in final print. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

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 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 a **MAJOR** amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-404

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

MAR 11 199

Dear Sir:

This is in reference to your abbreviated new drug application dated September 3, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act for Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

Reference is also made to your amendment dated November 8, 1993.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

PAGES 2-7 REMOVED
CONTAIN CHEMISTRY TRADE
SECRET INFORMATION

B. Labeling Deficiencies

COMMENTS: We note that your insert labeling is based on the 2/92 revision of the reference listed drug, Tenoretic® (Zeneca Pharmaceuticals). Significant and approved changes in the insert labeling of Tenoretic® were made in revisions 3/92 and 10/92 which are reflected in the changes requested below.

Container: Not Satisfactory

1. Increase the prominence of the drug name on the primary control panel of your container label.

2. Decrease the prominence of the "CAUTION: Federal law prohibits..." statement on your label.

3. We note that when the draft container labels for the 50 mg/25 mg and 100 mg/25 mg potencies are compared side by side, they appear very similar. We would encourage you to differentiate between the different potencies by using a contrasting color. We would be open to other suggestions that would improve product differentiation, which might result in reducing potential medication errors.

4. Allow the statement of storage conditions and the dispensing statement to the pharmacist to appear in consecutive order on the label.

Insert: Not Satisfactory

1. General:

   a. Put the degree symbol (°) by temperatures wherever this has not been done.

   b. We note that the product name is sometimes referred to as atenolol and chlorthalidone and sometimes as atenolol/chlorthalidone. Refer to the product name (atenolol and chlorthalidone) consistently throughout the insert.

   c. Revise the spacing between sections and paragraphs to be consistent throughout the insert.

2. Insert Title:

   Use lower case for "mg" in your insert title.

3. DESCRIPTION:

   a. Third line: "...agent (atenolol)...", (close parenthesis).

   b. Sentence beginning, "Chlorthalidone is...": "...(1-hydroxy-3-oxo-1-isoindolinyl)...", (close parenthesis).

c. For the chemical formula of chlorthalidone, remove subscript function on the (Cl) part of the molecule.

d. We note that your batch records list gelatin as an inactive ingredient. Please include gelatin in your description of inactive ingredients.

4. CLINICAL PHARMACOLOGY:

a. Pharmacodynamics:, paragraph beginning, "In controlled clinical trials,...":

"...combination resulting in a larger fall in blood pressure than with the single agents. The dose range...".

b. Pharmacokinetics and Metabolism:, second paragraph:

"...filtration rate; but significant...", (delete comma).

5. INDICATIONS AND USAGE:

a. First sentence: "Atenolol and chlorthalidone is indicated..."

b. Second sentence: Place a period at the end of the sentence.

6. CONTRAINDICATIONS:

Atenolol and chlorthalidone is contraindicated...".

7. WARNINGS:

a. In "Cardiac Failure:" subsection: "In patients who have congestive...", (delete the word "hypertensive").

b. In "Renal and Hepatic..." subsection: "Since atenolol is excreted...", (delete: "and chlorthalidone").

c. In "Ischemic Heart Disease:" subsection:

i) First sentence: "Following abrupt cessation...", (delete: "Although...atenolol").

ii) Last sentence: "...is common and may be unrecognized, it may...".

d. In "Anesthesia and Major Surgery:" subsection:

i) Replace first paragraph of section with:

"It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

ii) Delete the last sentence of this subsection: "Manifestations of...".

e. In "Metabolic and Endocrine Effects:" subsection:

i) Third sentence: "At recommended doses atenolol does not...".

ii) Separate the first paragraph into two paragraphs: "Insulin requirements in...", will be the beginning of the second paragraph.

f. Add the following as the last subsection:

Pregnancy and Fetal Injury: Atenolol and chlorthalidone can cause fetal harm when administered

to a pregnant woman. Atenolol and thiazides cross the placental barrier and appear in cord blood. No studies have been performed on the use of atenolol and chlorthalidone in the first trimester and the possibility of fetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol for longer periods to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation. If atenolol and chlorthalidone is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol and chlorthalidone was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no evidence of embryofetotoxicity observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. No teratogenic effects were noted, but embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose*). In the second rabbit study, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embyrotoxic effects were demonstrated.

Atenolol - Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or

25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

Chlorthalidone - Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

8. PRECAUTIONS

a. In the "Electrolyte and Fluid Balance Status:" subsection, third paragraph: "...intake of potassium is abnormally...".

b. In the "Drug Interactions:" subsection: replace the last sentence, "Should it..." with the following two paragraphs:

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

While taking beta blockers, patients with a history of

anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

c. In the "Carcinogenesis, Mutagenesis, Impairment of Fertility:" subsection:

i) Fifth line: "...antihypertensive dose*, did...".

ii) Seventh line: "...and 1500 mg/kg/day (250 and 750 times the maximum recommended antihypertensive dose*) resulting...".

iii) Line 11: "...in males. No...".

iv) Last sentence of first paragraph: "...Ames test (*S. typhimuyrium)*.", (add space, italicize microorganism name).

v) Delete second paragraph in the section: "Atenolol was negative...".

vi) Third paragraph: "...recommended human dose*) was...".

d. In the "Animal Toxicology:" subsection:

i) Fourth line: "...recommended human antihypertensive dose*). There...".

ii) Second paragraph, last sentence: "...human antihypertensive dose*) and..." and later in the same sentence: "...300 but not 150 mg atenolol/kg/day (150 and 75

times the maximum recommended antihypertensive dose*, respectively)."

iii) To end of subsection on its own line add:
*Based on the maximum dose of 100 mg/day in a 50 kg patient.

e. Revise the "Use in Pregnancy:" subsection to read:

Use in Pregnancy: Pregnancy Category D: See WARNINGS - Pregnancy and Fetal Injury.

(Text of subsection deleted.)

9. ADVERSE REACTIONS

a. "Atenolol" subsection:

i) Second sentence: "...was higher for both atenolol..."

ii) Delete "(see table below)" at the end of this section.

b. The table should immediately follow the "Atenolol" subsection. Please make the following changes to the table:

i) Underline the main titles in the table; Volunteered (U.S. Studies) and Total-Volunteered and Elicited (Foreign + U.S. Studies) and capitalize "Elicited" as above.

ii) Enclose the "n=..." statements in parenthesis, e.g., (n=164).

iii) Directly beneath each "n=..." statement, include: "%".

iv) Capitalize "Extremities" in the CARDIOVASCULAR group.

v) Below "Postural Hypotension" in the CARDIOVASCULAR group, add another row entitled "Leg

Pain" and enter the following values from left to right in the four columns: 0, 0.5, 3, and 1.

vi) In the RESPIRATORY group: capitalize "WARNINGS"

c. Revise the "Miscellaneous:" subsection to immediately follow the "Potential Adverse Effects" subsection.

d. In the paragraph following the table: "During postmarketing experience, the...", (include comma).

e. In the "Chlorthalidone:" subsection: "...CNS: vertigo, paresthesia,...".

f. In the "Potential Adverse Effects:" subsection make the following changes:

i) Revise the title to be represented as a subsection.

ii) "...decreased performance on neuropsychometrics and visual disturbance; Cardiovascular...".

iii) "...Hematologic: agranulocytosis; Allergic: erythematous rash...".

iv) "...and respiratory distress; Other: Raynaud's phenomenon."

v) Delete the last paragraph: "There have been...or atenolol.".

g. Insert the following text as a second paragraph to the "Miscellaneous:" subsection and immediately before the "Clinical Laboratory Test Findings:" subsection:

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

10. OVERDOSAGE

a. Revise the second sentence as follows: "Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal.".

b. Replace: "Therapy with atenolol/ chlorthalidone should...established procedures." with: "Atenolol can be removed from the general circulation by hemodialysis. further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.".

c. "Atenolol" subsection, Remove the sentence: "Atenolol can be removed from the general circulation by hemodialysis.".

d. In the "BRADYCARDIA:" section of the "Atenolol" subsection:

i) "Atropine 1-2 mg...", (Add a space).

ii) "...a transvenouos cardiac pacemaker..."

iii) "Glucagon in a 10 mg...", (Add a space).

iv) "...glucagon 1-10 mg/h...", (Add a space).

e. In the "HEART BLOCK" section of the "Atenolol" subsection: "(SECOND OR THIRD DEGREE)":, (capitalize).

f. In the "ELECTROLYTE IMBALANCE:" section of the "Atenolol" subsection:

i) Change this title to read: "ELECTROLYTE DISTURBANCE:"

ii) "Based on the severity..."

11. DOSAGE AND ADMINISTRATION

a. Change reference to atenolol and chlorthalidone tablets from 50 & 100 to 50 mg/25 mg & 100 mg/25 mg.

b. In the third paragraph: "...mL/min/1.73 m^2); therefore,...", (change comma to semicolon).

12. HOW SUPPLIED

a. First sentence: "Atenolol and chlorthalidone...", (lower case "c").

b. Separate the second paragraph into two paragraphs. "The tablets should be..." will be the beginning of the third paragraph.

Revise your container labels and insert labeling, then prepare and submit draft labeling.

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 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 a **MAJOR** amendment and should be so designated in your cover letter.

You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

3/10/94

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 74-404
DUP
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-647/LTang/2-15-94 3/3/94

HFD-613/CHoppes/2-28-94 3/3/94

HFD-647/JSimmons/2-22-94 3.4.94

HFD-617/TAmes/2-28-94 3/4/94

Initially reviewed 3/8/94

74404N01.LLT/2-15-94/disk #15

F/T LT/3-3-94

NOT APPROVABLE - Major

3/11/94