CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74657

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

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

Date of Review: October 24, 1996

Date of Submission: October 12, 1996

Primary Reviewer: Carol Holquist

ANDA Number: 74-657 **Review Cycle:** 4 - FPL

Applicant's Name [as seen on 356(h)]: Invamed Inc.

Established Name: Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: December 21, 1995 (100s, 500s and 1000s - 1 mg, 2 mg, 5 mg and 10 mg).

Professional Package Insert Labeling:	October 12, 1996 (Rev. September 1996).
Patient Information Insert Labeling:	October 12, 1996 (Rev. September 1996).

Revisions Needed Post Approval: Insert

a. CLINICAL PHARMACOLOGY

i. Pharmacodynamics, Benign Prostatic Hyperplasia, Paragraph 2 - ...men with symptomatic BPH. [Note: Delete "the".]

ii. Mean Changes in Blood Pressure Chart

Revise Normotensive heading to read "≤ 90 mm Hg" rather than "< 90 mm Hg" and Hypertensive Patients

to read "> 90 mm Hg" rather than "≥ 90 mm Hg".

b. PRECAUTIONS - Revise the subsection headings to be consistent with the other subsection headings throughout the text of the insert.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Hytrin® Tablets

NDA Number: 19-057 - This NDA was withdrawn from the orange book but has now been relisted.

NDA Drug Name: Hytrin® Tablets

NDA Firm: Abbott Laboratories

Date of Approval of NDA Insert and supplement #:
September 18, 1996/S-011

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: Hytrin labels in the file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.		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			
PROPRIETARY NAME			
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?			
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?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		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	
Error Prevention Analysis: *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.		X	
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.		X	
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. Model for insert is Hytrin Tablets (Abbott, revised 8/96, approved 9/18/96). Abbott has discontinued marketing the tablet and the application was withdrawn in the Orange Book. It has since been reinstated. According to the CSO Zelda McDonald the firm did not withdraw for safety/efficacy reasons.

2. Hytrin is covered by 5 patents. One patent expired on 5/31/94. Another relates to the dihydrate form and expires 2/17/00. Invamed claims their product (anhydrous) will not infringe this patent. One other patent relating to the use of terazosin hydrochloride in the treatment of hypertension expires 1/21/97 and another relating to the anhydrous polymorphic form expires 4/29/13. The two other patents refer to the use of stereo specific isomer in hypertension or BPH. Exclusivity for the treatment of BPH expires 9/29/96. The patent for use "hypertension" was to expire on September 5, 1995. It was extended by GATT until January 21, 1997. This GATT extension was the subject of a court case and apparently was denied, therefore it has been removed from the Orange Book. [See page vii of supplement #5). In supplement 5 of the Orange Book another patent for the tablets was added 5504207, which expires on April 29, 2013. According to Mary Ann Holovac this is a drug substance patent.

3. The listed drug, Hytrin, starts with the dihydrate form of the drug. The generic firms are proposing a product starting with an anhydrous form, claiming this does not infringe on the patent which expires 2/17/00.

4. OGD accepted the application for review based on previous actions that show we do not consider water of hydration a factor in determining generic equivalence.

5. Storage -

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

   NDA - Store below 86°F (30°C).

6. Invamed has revised the chemical name and the structural formula (to delete water) in the DESCRIPTION section. This is acceptable. It was decided by JGRACE, YMille, and JPhillips NOT to have generic firms, who use the anhydrous form, indicate the tablets were anhydrous [i.e., Each tablet contains terazosin hydrochloride (anhydrous)..], since the anhydrous form is hygroscopic and becomes hydrous during the process with the hydrous form actually in the final dosage form.

7. This product is not covered by a USP monograph. The USP - DI calls the product by the established name -

   Terazosin Hydrochloride Tablets

8. Both Hytrin and INVAMED's tablets are unscored.

9. The last amendment dealt with the Patient Information Insert. In the review dated July 22, 1996 we notified the firm that the tablets had been withdrawn and that the Capsules would now be the model labeling. The capsules contained a Patient Information Insert with the approved labeling. Therefore, we told the firm they needed to include an insert. I received a letter from the firm dated August 26, 1996 stating the tablets had been reinstated to the Orange Book and therefore made it the listed drug again and a patient insert would not be needed. However, on September 18, 1996 new labeling was approved for the Tablets that did include a patient information insert as part of the approved labeling. Therefore, we will request it from this firm.

10. This amendment contained final printed physician insert labeling and patient insert labeling.

/S/ — 10/25/96

Primary Reviewer — Date

/S/ — 10-25-96

Secondary Reviewer — Date

/S/ — 10/29/96

Team Leader JJ — Date

Labeling Review Branch

cc:

ANDA 74-657
Dup/Division File
HFD-613/CHolquist/DKonigstein/JGrace (no cc)

Review

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

Date of Review: September 23, 1996

Date of Submission: September 6, 1996

Primary Reviewer: Carol Holquist

Secondary Reviewer: John Grace

ANDA Number: 74-657 **Review Cycle:** 4 - Draft

Applicant's Name [as seen on 356(h)]: Invamed Inc.

Established Name: Terazosin Hydrochloride Tablets

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS

a. We acknowledge your correspondence dated August 26, 1996 confirming the relisting of terazosin hydrochloride tablets in Approved Drug Products as the referenced listed drug for the tablet formulation. However, since this correspondence, there has been new labeling approved for Hytrin Tablets (Abbott Laboratories; Approved September 18, 1996; Revised August 1996) that includes a "Patient Information Insert" as part of the approved labeling. Therefore, a patient information insert will be required.

b. In addition to the revised innovator labeling referenced above, the exclusivity for "Benign Prostatic Hyperplasia" expires on September 29, 1996. Therefore, we request you revise the draft insert labeling submitted on July 15, 1996 with the changes below.

2. INSERT

a. PHYSICIAN INSERT

i. CLINICAL PHARMACOLOGY

A) Pharmacodynamics, Hypertension

Paragraph 2, last sentence - Revise to read "measurements" rather than "measurement".

B) Pharmacokinetics

Paragraph one, first sentence - ...as terazosin tablets is...

ii. CONTRAINDICATIONS

...hypersensitive to terazosin hydrochloride.

iii. WARNINGS

Insert the following text to appear as the last subsection:

Priapism:
Rarely, (probably less than once in every several thousand patients), terazosin and other α_1-antagonists have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Two or three dozen cases have been reported. Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see PRECAUTIONS, Information for Patients).

iv. PRECAUTIONS

Information for Patients

A) Revise the subsection heading to read:

Information for Patients (see Patient Package Insert)

B) Insert the following text as the last paragraph of this subsection:

Patients should be advised about the possibility of priapism as a result of treatment with terazosin hydrochloride and other similar medications. Patients should know that this reaction to terazosin hydrochloride is extremely

rare, but that if it is not brought to immediate medical attention, it can lead to permanent erectile dysfunction (impotence).

v. ADVERSE REACTIONS

A) Benign Prostatic Hyperplasia, second paragraph below Table 1 - Revise the first sentence to read:

The adverse events were usually...

B) Hypertension

(1) Insert "HYPERTENSION" under the titles of tables 3 and 4.

(2) Insert the following text to appear as the last sentence of the second paragraph following "Table 1":

Post-marketing...administration of terazosin hydrochloride tablets. There have been reports of priapism during post-marketing surveillance.

(3) Insert a space prior to the section heading OVERDOSAGE.

vi. DOSAGE AND ADMINISTRATION

Hypertension - Delete the text under "Use with Other Drugs" and replace with "See above".

vii. Insert the following as the section following HOW SUPPLIED:

REFERENCE

1. Lepor H. Role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. *Prostate* 1990; 3:75-84.

b. PATIENT INFORMATION INSERT

WARNINGS

Insert the following text to appear as the last paragraph:

Extremely rarely, terazosin and similar

medications have caused painful erection of the penis, sustained for hours and unrelieved by sexual intercourse or masturbation. This condition is serious, and if untreated it can be followed by permanent inability to have an erection. If you have a prolonged abnormal erection, call your doctor or go to an emergency room as soon as possible.

Please revise your labeling, as instructed above, and submit 12 final printed patient package inserts and patient information inserts. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: December 21, 1995 (100s, 500s and 1000s - 1 mg, 2 mg, 5 mg and 10 mg).

Professional Package Insert Labeling:

Patient Information Insert Labeling:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Hytrin Tablets

NDA Number: Used to be 19-057 - This NDA was withdrawn from the orange book but has now been relisted.

NDA Drug Name: Hytrin Tablets

NDA Firm: Abbott Laboratories

Date of Approval of NDA Insert and supplement #:
September 18, 1996/S-011

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: Hytrin labels in the file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.		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			
PROPRIETARY NAME			
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?			
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?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		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	

Error Prevention Analysis: *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.		X	
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.		X	
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. Model for insert is Hytrin Tablets (Abbott, revised 8/96, approved 9/18/96). Abbott has discontinued marketing the tablet and the application was withdrawn in the Orange Book. According to the CSO Zelda McDonald the firm did not withdraw for safety/efficacy reasons. It has since been reinstated.

2. Hytrin is covered by 5 patents. One patent expired on 5/31/94. Another relates to the dihydrate form and expires 2/17/00. Invamed claims their product (anhydrous) will not infringe this patent. One other patent relating to the use of terazosin hydrochloride in the treatment of hypertension expires 1/21/97 and another relating to the anhydrous polymorphic form expires 4/29/13. The two other patents refer to the use of stereo specific isomer in hypertension or BPH. Exclusivity for the treatment of BPH expires 9/29/96. The patent for use "hypertension" was to expire on September 5, 1995. It was extended by GATT until January 21, 1997. This GATT extension was the subject of a court case and apparently was denied, therefore it has been removed from the Orange Book. [See page vii of supplement #5). In supplement 5 of the Orange Book another patent for the tablets was added 5504207, which expires on April 29, 2013. According to Mary Ann Holovac this is a drug substance patent. Since it is so close to the expiration of the BPH exclusivity, I have decided to retain the BPH information in the labeling. This application is also waiting for a methods validation.

3. The listed drug, Hytrin, starts with the dihydrate form of the drug. The generic firms are proposing a product starting with an anhydrous form, claiming this does not infringe on the patent which expires 2/17/00.

4. OGD accepted the application for review based on previous actions that show we do not consider water of hydration a factor in determining generic equivalence.

5. Storage -

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

   NDA - Store below 86°F (30°C).

6. Invamed has revised the chemical name and the structural formula (to delete water) in the DESCRIPTION section. This is acceptable. It was decided by JGRACE, YMille, and JPhillips NOT to have generic firms, who use the anhydrous form, indicate the tablets were anhydrous [i.e., Each tablet contains terazosin

hydrochloride (anhydrous)..], since the anhydrous form is hygroscopic and becomes hydrous during the granulation process with the hydrous form actually in the final dosage form.

7. This product is not covered by a USP monograph. The USP - DI calls the product by the established name -

   Terazosin Hydrochloride Tablets

8. Both Hytrin and INVAMED's tablets are unscored.

9. This amendment dealt with the Patient Information Insert. In the last review we notified the firm that the tablets had been withdrawn and that the Capsules would now be the model labeling. The capsules contained a Patient Information Insert with the approved labeling. Therefore, we told the firm they needed to include an insert. I received a letter from the firm dated August 26, 1996 stating the tablets had been reinstated to the Orange Book and therefore made it the listed drug again and a patient insert would not be needed. However, on September 18, 1996 new labeling was approved for the Tablets that did include a patient information insert as part of the approved labeling. Therefore, we will request it from this firm.

/S/

Primary Reviewer — Date

/S/

Team Leader
Labeling Review Branch — 9-27-96 Date

cc:

ANDA 74-657
Dup/Division File
HFD-613/CHolquist/AVezza/JGrace (no cc)

Review

RECORD OF TELEPHONE CONVERSATION

DATE: August 12, 1996, 10:30 AM & 11 AM

PRODUCT NAME: Terazosin Hydrochloride Tablets

ANDA/AADA NUMBER: 74-657

FIRM NAME: Invamed, Inc.
Dayton, NJ

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD:

Dr. Mahendra Patel, Vice-President, Invamed
Mr. M. Smela Jr. Team Leader, ANDA Review Branch II
Mr. S. Sherken, Review Chemist, ANDA Review Branch II

PARTICIPANT(S) TELEPHONE:

Dr. Patel 908-274-2400
Mr. Smela & Mr. Sherken 301-594-0370

MINUTES OF CONVERSATION:

Mr. Smela contacted Dr. Patel to discuss their specification of Total Degradants/Impurities for the Drug Product and Stability of Terazosin Tablets. Invamed proposed a specification of NMT % for Total Degradants/Impurities. Based on the data of the four strengths of tablets, we felt that the specification could be lowered somewhat and we asked Dr. Patel to do so.

Dr. Patel said that he would like to review their data first before they would recommend a change. At this point the conversation ended.

At about 11 AM, Dr. Patel called back and recommended a specification of NMT %. Mr. Smela told him to submit this change in a TELEPHONE amendment to the ANDA, with a FAX to Mr. Sherken. Dr. Patel agreed to do this.

Then Dr. Patel told us that the New Jersey District had several months ago, sent a investigator to pick up a sample for methods validation. We informed him that we were also trying to track down the sample, and the completed validation report. So far we have been unsuccessful in our endeavor. Dr. Patel said that he would try to track it down. At that point the conversation ended.

/S/ 8/12/96
Mr. Michael J. Smela Jr.
Team Leader, ANDA Review Branch II

/S/ 8/12/96
Mr. Stephen Sherken
Review Chemist, ANDA
Review Branch II

August 12, 1996