

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40301

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 40-301 Date of Submission: May 27, 1999

Applicant's Name: Taro Pharmaceuticals USA Inc.

Established Name: Warfarin Sodium Tablets USP, 1 mg, 2 mg,
2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 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: 100s - 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg,
5 mg, 6 mg, 7.5 mg, 10 mg
1000s - 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg,
5 mg, 6 mg

Satisfactory in FPL as of September 29, 1998 submission.

Professional Package Insert Labeling:

Satisfactory in FPL as of May 27, 1999 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: Coumadin®

NDA Number: 09-218

NDA Drug Name: Coumadin® (Warfarin Sodium USP) Tablets,

NDA Firm: DuPont Merck

Date of Approval of NDA Insert and supplement #: 6-1-98 (S-086,
S-090, S-091)

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: side-by-sides

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	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
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	
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	
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 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: (portions taken from previous review)

1. Model for insert is Coumadin® (DuPont Merck, approved June 1, 1998, revised April, 1998, NDA 09-218/S-086, 090, 091).
2. There are no patents or exclusivities remaining on Coumadin. In recent years, Coumadin has received approval for 2 new indications, but no exclusivities were granted. This was confirmed with M.Holovac in DDIR. The firm's statement is accurate.
3. Scoring is the same as innovator, all strengths scored.
4. Storage -
 - NDA - Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C).
 - ANDA - Protect from light. Store at controlled room temperature 15°-30°C (59°-86°F).
5. Dispensing -
 - ANDA, NDA, and USP - T, LR.

6. The following is from a previous review on ANDA 40-145 ,Barr Co.).

Regarding the comments on "delete the asterisk following the established name" and "Delete Present as crystalline sodium warfarin isopropanol clathrate" from the container labels - This was discussed by JPhillips and JGrace and it was decided to delete for generic firms, since it is not necessary to clarify product strength and otherwise not meaningful. The PI, DESCRIPTION section does mention "crystalline".

7. All inactives are accurately listed in the DESCRIPTION section of the insert labeling. See page 6490, Vol.B. 1.1.

8. This product will be packaged in opaque white HDPE bottles with Child-proof safety cap. See page 7613, Vol.B. 1.4.

9. The description of the tablets in the HOW SUPPLIED section of the insert is correct. See pages 7724-7732 in vol.B.1.4

10. The color of each tablet of different strength is consistent with that of the innovator's except the strength of 3 mg, 5 mg, & 6 mg. There is no legal requirement that the color of the generic product should be based on the innovator's. The innovator makes 1 mg in pink and 5 mg in peach color, and due to the similarity of these two colors, there have been incidents where the patients took wrong strength tablet resulting in death induced by overdose. (See FTR for Warfarin sodium tablets). The sponsor of this generic drug uses pink for 1 mg and orange for 5 mg, in an apparent effort to further differentiate these two strengths. We find this acceptable.

11. The firm has included per Agency's request the first two sentences of the "Intravenous Route of Administration" subsection under the "DOSAGE AND ADMINISTRATION" section. These two sentences include general information regarding conversion of oral drug to IV drug in terms of dosage.

Date of Review: 6-14-99 Date of Submission: 5-27-99

Primary Reviewer: Adolph Vezza

Date:

IS/

6/15/99

Team Leader: Charlie Hoppes

Date:

IS/

6/15/99

IS/

6/15/99

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

ANDA Number: 40-301 Date of Submission: September 29, 1998

Applicant's Name: Taro Pharmaceuticals USA Inc.

Established Name: Warfarin Sodium Tablets USP, 1 mg, 2 mg,
2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg

Labeling Deficiencies:

INSERT

a. GENERAL

- i. We note that you have not complied fully with the instructions in the Agency's last deficiency letter. Refer to the following comments for detail.
- ii. We note that your typed draft version of your insert used for the side-by-side comparison is not identical to the insert submitted in computer generated printer's proof. Please note that the following comments are based upon your insert submitted in computer generated printer's proof.

b. WARNINGS

- i. Second paragraph, penultimate sentence:
...the one stage PT. [rather than "PT/INR."]
- ii. Include the following subsection heading and text immediately preceding the seventh paragraph "A severe elevation...".

Heparin-induced thrombocytopenia: Warfarin should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or

continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

c. PRECAUTIONS

- i. Replace "Warfarin Sodium Tablets, USP" with "warfarin" throughout the text.
- ii. Fourth paragraph - **The following factors, alone or in combination, may be responsible for INCREASED PT or INR response:** Exogenous Factors:

A) Relocate the followings in the list of "specific drugs reported" to the appropriate places based on the alphabetical order.

fluconazole, fluorouracil

B) Relocate the following classes in the list of "specific drugs reported" to be in alignment with the left margin.

Ibuprofen, indomethacin, methimazole†

C) The paragraph beginning with "also; other..." at the end of the table:

...unreliable PT/INR determinations [rather than "PT"]

- iii. Fifth paragraph - **The following factors, alone or in combination, may be responsible for DECREASED PT or INR response:**

...DECREASED PT/INR response: [rather than "PT or INR"]

d. ADVERSE REACTIONS

- i. See comment (i) under PRECAUTIONS.
- ii. Potential adverse reactions... include - Fourth item:

... infrequently include:
hypersensitivity/allergic reactions, systemic...

e. OVERDOSAGE

See comment (i) under PRECAUTIONS.

f. DOSAGE AND ADMINISTRATION

i. First paragraph:

... for full discussion on INR. [rather than "PT/INR"]

ii. The sentence immediately prior to the "Initial Dosage" subsection.

An INR of greater than 4 appears to ...

iii. Initial Dosage:

A) Delete the term "ratio" to read "PT/INR" rather than "PT/INR ratio" in two instances.

B) Revise the third sentence to read as follows: -

... with potential to exhibit greater than expected PT/INR response to warfarin sodium tablets, USP (see PRECAUTIONS). It is...

iv. Laboratory Control:

A) First paragraph, fourth sentence:

The PT should be... [rather than "PT/INR"]

B) First paragraph, fifth sentence:

Intervals between subsequent PT/INR determinations... [rather than "PT"]

C) Fourth paragraph:

Delete one line space in the first sentence.

v. Table 3

Lighten the background so that the contrast becomes sufficient.

vi. CONVERSION FROM HEPARIN THERAPY - Last sentence:

...the desired PT/INR or prothrombin...

continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

c. PRECAUTIONS

- i. Replace "Warfarin Sodium Tablets, USP" with "warfarin" throughout the text.
- ii. Fourth paragraph - **The following factors, alone or in combination, may be responsible for INCREASED PT or INR response:** Exogenous Factors:

A) Relocate the followings in the list of "specific drugs reported" to the appropriate places based on the alphabetical order.

fluconazole, fluorouracil

B) Relocate the following classes in the list of "specific drugs reported" to be in alignment with the left margin.

Ibuprofen, indomethacin, methimazole†

C) The paragraph beginning with "also; other..." at the end of the table:

...unreliable PT/INR determinations [rather than "PT"]

- iii. Fifth paragraph - **The following factors, alone or in combination, may be responsible for DECREASED PT or INR response:**

...DECREASED PT/INR response: [rather than "PT or INR"]

d. ADVERSE REACTIONS

- i. See comment (i) under PRECAUTIONS.
- ii. Potential adverse reactions... include - Fourth item:

... infrequently include:
hypersensitivity/allergic reactions, systemic...

Please revise your package 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.

Robert L. West, M.S., R.Ph.
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 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.		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)			
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 C _{max} , T _{max} , T ½ 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.			

NOTES/QUESTIONS TO THE CHEMIST:

According to the firm's Statement of Composition, each tablet has approximately 10 % overage of active ingredient as compared to the actual strengths of the tablets. Is it acceptable? I believe the strength on the labels and labeling should represent the actual amount of warfarin sodium. Can you help me with issue? Thank you for your help. (e-mail sent to the chemist Andrew Langowski on 6/26/98 and 12/28/98 to address this question)

Answer from Andrew Langowski (1/4/98):

This is a CMC issue and not a labeling issue, but I'll take a few minutes to enlighten you.

It's not uncommon to manufacture a drug product (whether it be

solid oral, solution or parenteral) with an excess of active ingredient. This is usually done because of a unique characteristic of the components used or the manufacturing process. If the tested product meets release specs. then there is not a problem.

Regarding label strength, consider the following statement. The final product almost never exactly contains the labeled amount of active ingredient.

Why is this?

Because the firm is only required to meet the final product specification. The most common monograph spec for potency of the active is 90.0-110.0% (i.e., If the labeled amount were 5 mg. The firm could in actuality release product containing as little as 4.5 mg or as much as 5.5 mg and neither precisely meets the label, but is acceptable.

Andrew

FOR THE RECORD:

1. Model for insert is Coumadin® (DuPont Merck, approved June 1, 1998, revised April, 1998, NDA 09-218/S-086, 090, 091).
2. There are no patents or exclusivities remaining on Coumadin. In recent years, Coumadin has received approval for 2 new indications, but no exclusivities were granted. This was confirmed with M.Holovac in DDIR. The firm's statement is accurate.
3. Scoring is the same as innovator, all strengths scored.
4. Storage -
NDA - Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C).
ANDA - Protect from light. Store at controlled room temperature (59°-86°F, 15°-30°C).
5. Dispensing -
ANDA, NDA, and USP - T,LR.
6. The following is from a previous review on ANDA 40-145 (Barr Co.).

Regarding the comments on "delete the asterisk following the

established name" and "Delete Present as crystalline sodium warfarin isopropanol clathrate" from the container labels - This was discussed by JPhillips and JGrace and it was decided to delete for generic firms, since it is not necessary to clarify product strength and otherwise not meaningful. The PI, DESCRIPTION section does mention "crystalline".

7. All inactives are accurately listed in the DESCRIPTION section of the insert labeling. See page 6490, Vol.B. 1.1.
8. This product will be packaged in opaque white HDPE bottles with Child-proof safety cap. See page 7613, Vol.B. 1.4.
9. The description of the tablets in the HOW SUPPLIED section of the insert is **correct**. See pages 7724-7732 in vol.B.1.4
10. The color of each tablet of different strength is consistent with that of the innovator's except the strength of 3 mg, 5 mg, & 6 mg. There is no legal requirement that the color of the generic product should be based on the innovator's. The innovator makes 1 mg in pink and 5 mg in peach color, and due to the similarity of these two colors, there have been incidents where the patients took wrong strength tablet resulting in death induced by overdose. (See FTR for Warfarin sodium tablets). The sponsor of this generic drug uses pink for 1 mg and orange for 5 mg, in an apparent effort to further differentiate these two strengths. We find this acceptable.
11. The firm has included per Agency's request the first two paragraphs of the "Intravenous Route of Administration" subsection under the "DOSAGE AND ADMINISTRATION" section. These two paragraphs include general information regarding conversion of oral drug to IV drug in terms of dosage.

Date of Review: December 29, 1998

Date of Submission:
September 29, 1998

Primary Reviewer: Chan park

Date: 2/11/99

Team Leader: Charlie Hoppes

Date:

cc:

ANDA: 40-301
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)

Review

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

ANDA Number: 40-301 Date of Submission: April 30, 1999

Applicant's Name: Taro Pharmaceuticals USA Inc.

Established Name: Warfarin Sodium Tablets USP, 1 mg, 2 mg,
2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg

Labeling Deficiencies:

INSERT

1. GENERAL COMMENT

We acknowledge your comment that you have submitted "FPL" labels and labeling but please note that for insert labeling to be in final print the text of the insert must appear on one continuous sheet of paper.

2. PRECAUTIONS

Exogenous Factors - ... with warfarin sodium are ...
(two locations)

3. DOSAGE AND ADMINISTRATION

Table 3

Lighten the background shading so that the contrast becomes sufficient.

4. HOW SUPPLIED

There is the statement "Store in carton until contents have been used." present but you have not supplied carton labeling. Please comment.

Please revise your 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. . .

Robert L. West, M.S., R.Ph.
Director
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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 100s - 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg,
5 mg, 6 mg, 7.5 mg, 10 mg
1000s - 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg,
5 mg, 6 mg

Satisfactory in FPL as of September 29, 1998 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? NO

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

NDA Number: 09-218

NDA Drug Name: Coumadin® (Warfarin Sodium USP) Tablets,

NDA Firm: DuPont Merck

Date of Approval of NDA Insert and supplement #: 6-1-98 (S-086,
S-090, S-091)

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: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	F.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	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
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	
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	
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Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
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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 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 C _{max} , T _{max} , T 1/2 and data 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	
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4. Storage -
 - NDA - Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C).
 - ANDA - Protect from light. Store at controlled room temperature 15°-30°C (59°-86°F).
5. Dispensing -
 - ANDA, NDA, and USP - T,LR.
6. The following is from a previous review on ANDA 40-145 (Barr Co.).

Regarding the comments on "delete the asterisk following the established name" and "Delete Present as crystalline sodium warfarin isopropanol clathrate" from the container labels - This was discussed by JPhillips and JGrace and it was decided to delete for generic firms, since it is not necessary to clarify product strength and otherwise not meaningful. The PI, DESCRIPTION section does mention "crystalline".
7. All inactives are accurately listed in the DESCRIPTION section of the insert labeling. See page 6490, Vol.B. 1.1.
8. This product will be packaged in opaque white HDPE bottles with Child-proof safety cap. See page 7613, Vol.B. 1.4.
9. The description of the tablets in the HOW SUPPLIED section of the insert is **correct**. See pages 7724-7732 in vol.B.1.4

10. The color of each tablet of different strength is consistent with that of the innovator's except the strength of 3 mg, 5 mg, & 6 mg. There is no legal requirement that the color of the generic product should be based on the innovator's. The innovator makes 1 mg in pink and 5 mg in peach color, and due to the similarity of these two colors, there have been incidents where the patients took wrong strength tablet resulting in death induced by overdose. (See FTR for Warfarin sodium tablets). The sponsor of this generic drug uses pink for 1 mg and orange for 5 mg, in an apparent effort to further differentiate these two strengths. We find this acceptable.
11. The firm has included per Agency's request the first two sentences of the "Intravenous Route of Administration" subsection under the "DOSAGE AND ADMINISTRATION" section. These two sentences include general information regarding conversion of oral drug to IV drug in terms of dosage.

Date of Review: 5-12-99 Date of Submission: 4-30-99

Primary Reviewer: Adolph Vezza Date:

/S/

5/25/99

Team Leader: Charlie Hoppes Date:

/S/

5/25/99

cc:

ANDA: 40-301
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review

RECORD OF TELEPHONE CONVERSATION

DATE: May 26, 1999

ANDA: 40-301

DRUG PRODUCT: Warfarin

FIRM: Taro

CONVERSATION WITH: Lorraine Sachs

PHONE NUMBER: 914-345-9001

TOPIC: Boxing of tables and lists

Ms. Lorraine Sachs of Taro asked whether the boxing of lists and tables throughout the labeling could be deleted? I informed her that I would check with my teamleader and if they are required to have the boxing format, I would call her. If not required, I wouldn't call her.

After discussing this issue with Charlie, it was decided that the boxing was not need for this labeling.

Koung Lee

Document Room,
Please file
in Jacket.
Thanks
40-301 *ell*

ell - 5/26/99

RECORD OF TELEPHONE CONVERSATION

DATE: April 28, 1999
ANDA: 40-301
DRUG PRODUCT: Warfarin
MANUFACTURER: Taro
CONVERSATION WITH: Ms. Loraine Sax
PHONE NUMBER: 914-345-9001
TOPIC: PT/INR

Ms. Loraine Sax said that they mistakenly added "PT/INR" instead of just "INR" in the fifth paragraph in the "Clinical Trials" subsection of the CLINICAL PHARMACOLOGY section. I informed her that it should just be "INR" in that paragraph according to the last approved labeling supplement for the reference listed drug.

Koung Lee

KL
4/28/99

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

ANDA Number: 40-301 Date of Submission: March 2, 1998

Applicant's Name: Taro Pharmaceuticals USA Inc.

Established Name: Warfarin Sodium Tablets USP, 1 mg, 2 mg,
2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site <http://www.fda.gov/cder/guidance/index.htm>. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

2. CONTAINER

- a. See general comments.
- b. You may delete the statement
- c. We encourage you to differentiate your drug products of different strengths by using contrasting colors (preferably based on the color of the tablet) and/or using boxing, or some other means.
- d. Please assure that the text on the labels appear clearly legible.
- e. Revise the storage requirement to read "Store at controlled room temperature 15° - 30°C (59° -

86°F)".

- f. We note that you have not proposed carton labeling. Delete the statement and/or comment.
- g. Delete the asterisk following the established name and the text "*Present as crystalline sodium warfarin isopropanol clathrate." from the container labels

3. INSERT

a. GENERAL

- i. Please note that the labeling of the reference listed drug was last approved June 1, 1998. The following comments are based on this latest innovator's labeling. Other editorial comments are also made.
- ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or on the title of the package insert.
- iii. It is preferable to use "2.5 mg" and "7.5 mg" rather than respectively throughout the text as appears on the container labels.
- iv. Replace with "PT/INR" throughout the text except in the "Laboratory Control" subsection under DOSAGE AND ADMINISTRATION section.

b. DESCRIPTION

- i. First paragraph, second sentence:
... 4-hydroxycoumarin sodium salt and is...
- ii. First paragraph, last sentence:
...molecular formula is ... [rather than
- iii. We encourage the inclusion of the molecular weight.

- iv. Identify the botanical source for starch.
[i.e., corn starch]
- v. Revise to read "Anhydrous lactose"

c. CLINICAL PHARMACOLOGY

- i. Metabolism - Last sentence:

... the *in vivo* anticoagulant... [italic]

- ii. Clinical Trials

- A) Reduce the prominence of the subsection headings of this subsection so that they are differentiated from subsection headings.

- B) Myocardial Infarction - Table

- (1) Include title "TABLE 2" in the table.

- (2) Relocate the items in the first row so that they are aligned with the appropriate columns.

- C) Mechanical and Bioprosthetic Heart Valves:

Delete the entire last paragraph.

- d. CONTRAINDICATIONS (Miscellaneous) - Revise to read as follows:

... anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

- e. WARNINGS

- i. Replace "warfarin" throughout the text. with

- ii. Third paragraph:

... hemorrhage, necrosis, and/or gangrene is present.

- iii. Include the following subsection heading and text immediately preceding the seventh paragraph "A severe elevation...".

Heparin-induced thrombocytopenia: Warfarin should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

- iv. Seventh paragraph:

Delete the last sentence "This has been...".

- v. Lactation

- A) First sentence:

Warfarin appears...

- B) Last sentence - Revise to read as follows:

Infants nursed by mothers treated with warfarin sodium had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.

- vi. Miscellaneous - Fourth paragraph:

...failure may exhibit greater than expected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

- vii. Fifth paragraph:

Concomitant use...

f. PRECAUTIONS

- i. See comment (i) under WARNINGS.
- ii. Print the first four paragraphs in bold face type.
- iii. Fourth paragraph - The following factors, alone or in combination, may be responsible for **INCREASED PT or INR** response: Exogenous Factors:

- A) Include the following classes in the list of "classes of drugs" in the appropriate places based on the alphabetical order.

5-lipoxygenase Inhibitor, Antiandrogen,
Leukotriene Receptor Antagonist,
Selective Serotonin Reuptake Inhibitors

- B) Relocate the following classes in the list of "classes of drugs" to be in alignment with the left margin.

Hepatotoxic Drugs, Tuberculosis Agents,
Uricosuric Agents

- c) Include the following drugs in the list of "specific drugs reported" in the appropriate places based on the alphabetical order.

azithromycin, fluoxetine, flutamide,
fluvoxamine, zafirlukast, zileuton

- D) Relocate the followings in the list of "specific drugs reported" to the appropriate places based on the alphabetical order.

vitamin E, warfarin overdose, valproate

- E) Relocate the following classes in the list of "specific drugs reported" to be in alignment with the left margin.

olsalazine, oxaprozin, oxymetholone,
valproate, vitamin E, warfarin overdose

- iv. Fifth paragraph - The following factors, alone or in combination, may be responsible for **DECREASED PT or INR** response: Exogenous Factors:

Include "6-mercaptopurine" in the list of "specific drugs reported" after "meprobamate".

- v. Information for Patients - Add the following in bold face type as the last sentence in this subsection:

Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.

- g. **ADVERSE REACTIONS**

- i. See comment (i) under WARNINGS.
- ii. Revise the fifth paragraph to read as follows:

Adverse reactions reported... purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritis, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

- h. **OVERDOSAGE**

See comment (1) under WARNINGS.

- i. **DOSAGE, ADMINISTRATION, AND LABORATORY CONTROL**

- i. Revise the section heading to read "DOSAGE AND ADMINISTRATION".
- ii. In addition to the general comment (iv) under INSERT, revise the terms "the INR and/or PT ratio" to read "PT/INR". [two incidences]

iii. First paragraph:

... particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR (See...)

iv. Venous Thromboembolism (including pulmonary embolism) - Include the following as the last sentence:

In patients, with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman et al, 1995 and Schulman et al, 1997).

v. Atrial Fibrillation:

Delete the last sentence.

vi. Include the following subsection immediately prior to the "Laboratory control" subsection:

Intravenous Route of Administration: Warfarin sodium for injection provides an alternate administration route for patients who cannot receive oral drugs. The IV dosage would be the same as those that would be used orally if the patient could take the drug by the oral route.

vii. Laboratory Control

A) Revise the prominence of this subsection heading to be consistent with other subsection headings.

B) First paragraph, fourth and penultimate sentences:

Replace with "PT/INR".

C) First paragraph, last sentence - Revise to read as follows:

...interchanged with warfarin sodium tablets, USP, as well as whenever other

medications are initiated, discontinued, or taken irregularly (See PRECAUTIONS).

D) Last paragraph:

... is shown in Table 3.⁵ [rather than "Table 2"]

E) Table 2:

Revise to read "Table 3".

viii. Treatment During Dentistry and Surgery -
Fifth sentence:

..., dental and minor surgical procedures...

j. HOW SUPPLIED

i. We note that the color descriptions of the 3 mg and 5 mg strengths are not consistent with your Controls for Finished Dosage Form statements. Please revise accordingly and/or comment.

ii. We note that the engraving description of the 2 mg, 2.5 mg, 3 mg, 6 mg, and 7.5 mg are not consistent with your Controls for Finished Dosage Form statements. Please revise accordingly and/or comment.

iii. Penultimate paragraph:

..., as described in the above table, ...

iv. See comments (d) & (e) under CONTAINER.

v. See GENERAL COMMENTS.

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

Jerry Phillips
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 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.		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.		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 C _{max} , T _{max} , 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.			

NOTES/QUESTIONS TO THE CHEMIST:

According to the firm's Statement of Composition, each tablet has approximately 10 % overage of active ingredient as compared to the actual strengths of the tablets. Is it acceptable? I believe the strength on the labels and labeling should represent the actual amount of warfarin sodium. Can you help me with issue? Thank you for your help. (e-mail sent to the chemist Andrew Langowski on 6/26/98 to address this question)

Warfarin calcium salt is used, equivalent to warfarin. Not really 10% overage. AL

FOR THE RECORD:

1. Model for insert is Coumadin® (DuPont Merck, approved June 1, 1998, revised April, 1998, NDA 09-218/S-086, 090, 091).
2. There are no patents or exclusivities remaining on Coumadin. In recent years, Coumadin has received approval for 2 new indications, but no exclusivities were granted. This was confirmed with M.Holovac in DDIR. The firm's statement is accurate.
3. Scoring is the same as innovator, all strengths scored.
4. Storage -

NDA - Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C).

ANDA - Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C).

The applicant has not proposed carton and therefore, we will ask the firm to delete the reference to the carton.

5. Dispensing -

ANDA, NDA, and USP - T, LR.

6. The following is from a previous review on ANDA 40-145 (Barr Co.).

Regarding the comments on "delete the asterisk following the established name" and

from the container labels -

This was discussed by JPhillips and JGrace and it was decided to delete for generic firms, since it is not necessary to clarify product strength and otherwise not meaningful. The PI, DESCRIPTION section does mention "crystalline".

7. All inactives are accurately listed in the DESCRIPTION section of the insert labeling. See page 6490, Vol.B. 1.1.
8. This product will be packaged in opaque white HDPE bottles with Child-proof safety cap.. See page 7613, Vol.B. 1.4.
9. The description of the tablets in the HOW SUPPLIED section of the insert is in **NOT correct**. See comments (i) & (ii)

under HOW SUPPLIED section and pages 7724-7732 in vol.B.1.4

10. The color of each tablet of different strength is consistent with that of the innovator's except the strength of 3 mg, 5 mg, & 6mg. There is no legal requirement that the color of the generic product should be based on the innovator's. The innovator makes 1 mg in pink and 5 mg in peach color, and due to the similarity of these two colors, there have been incidents where the patients took wrong strength tablet resulting in death induced by overdose. (See FTR for Warfarin sodium tablets). The sponsor of this generic drug uses pink for 1 mg and orange for 5 mg, in an apparent effort to further differentiate these two strengths. We find this acceptable.
11. We will ask the firm to include the first two paragraphs of the "Intravenous Route of Administration" subsection under the "DOSAGE AND ADMINISTRATION" section. These two paragraphs include general information regarding conversion of oral drug to IV drug in terms of dosage.

Date of Review: June 26, 1998

Date of Submission: March 2, 1998

Primary Reviewer: Chan park

/S/

Date:

8/27/98

Team Leader: Charlie Hoppes

Date:

/S/

8/31/98

cc:

ANDA: 40-301
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)

Review