CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 09218/S086/S090/S091

Trade Name: COUMADIN TABLETS AND INJECTION

Generic Name: WARFARIN SODIUM

Sponsor: DUPONT MERCK PHARMACEUTICALS, INC.

Approval Date: 6/1/98

Indication(s): FOR THE PROPHYLAXIS AND/OR TREATMENT OF VENOUS THROMBOSIS
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</table>
Application Number: 09218/S086/S090/S091
The DuPont Merck Pharmaceuticals Inc.
Attention: Ms. Maida S. Burka
DuPont Merck Plaza
Maple Run
Wilmington, DE 19805

Dear Ms. Burka:

Please refer to your supplemental new drug applications dated submitted August 16, 1996 (S-086), December 31, 1997 (S-090), and May 7, 1998 (S-091), received August 19, 1996, January 2, 1998, and May 8, 1998 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coumadin® (Warfarin Sodium Tablets, USP) Tablets and Coumadin® (Warfarin Sodium for Injection, USP) for Injection.

We acknowledge receipt of your submissions dated May 20, 1998 for S-086, S-090, and S-091; May 7, 1998 for S-086 and S-090; and January 27, July 10, September 3, and December 31, 1997 for S-086.

These supplemental applications provide for revisions to the following sections of the package insert: (1) the DOSAGE AND ADMINISTRATION section, “Venous Thromboembolism (including pulmonary embolism)” subsection (S-086); (2) the CLINICAL PHARMACOLOGY section, “Clinical Trials” subsection (“Atrial Fibrillation”, “Myocardial Infarction”, and “Mechanical and Bioprosthetic Heart Valves” sub-subsections and Table 2), the WARNINGS section, “Lactation” subsection, the PRECAUTIONS section, “Exogenous Factors (increase PT/INR response)”, “Specific Drugs Reported” list, and the DOSAGE AND ADMINISTRATION section, “Post-Myocardial Infarction” subsection (S-090); and the CLINICAL PHARMACOLOGY section, “Clinical Trials” subsection (“Myocardial Infarction” sub-subsection), the WARNINGS section, the PRECAUTIONS section, “Exogenous Factors (increase PT/INR response)”, “Classes of Drugs” list and “Information to Patients” subsections, DOSAGE AND ADMINISTRATION section, “Laboratory Control” subsection, and the HOW SUPPLIED section (S-091).

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed labeling submitted on May 7, 1998.
(FPL “64660-01/Rev.April, 1998”) and May 20, 1998 (FPL “6193-18/Rev.April, 1998”). Accordingly, these supplemental applications are approved effective on the date of this letter. Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. If you have any questions, please contact Karen Oliver, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/Signature/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
cc: Original NDA 09/218-S-086
    Original NDA 09/218-S-090
    Original NDA 09/218-S-091
    HFD-180/Div. files
    HFD-180/K.Oliver
    HFD-180/E.Duffy
    HFD-180/M.Ysern
    HFD-180/L.Talarico
    DISTRICT OFFICE
    HF-2/Medwatch (with labeling)
    HFD-92/DDM-DIAB (with labeling)
    HFD-40/DDMAC (with labeling)
    HFD-613/OGD (with labeling)
    HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
    HFD-560/OTC (with labeling - for OTC Drug Products Only)
    HF-20/Press Office (with labeling)
Drafted by: KO/June 1, 1998 /S/ 06/01/98
final: KO/06/01/98/c:\mydocuments\NDA0921806-01-98-AP
APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09218/S086/S090/S091

FINAL PRINTED LABELING
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09218/S086/S090/S091

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 09-218/S-086 and S-090

Name of Drug: Coumadin® (Warfarin Sodium Tablets, USP) Tablets
Coumadin® (Warfarin Sodium for Injection, USP) for Injection

Sponsor: The DuPont Merck Pharmaceutical Company

Material Reviewed

Submission Date(s): December 31, 1997

Receipt Date(s): January 2, 1998

Background and Summary Description: In response to an August 28, 1997 approvable letter, the firm submitted final printed labeling. The labeling provides for revisions to the DOSAGE AND ADMINISTRATION section, the "Venous Thromboembolism (including pulmonary embolism)" subsection. Included in the full response amendment to S-086 is a "Special Supplement-Changes Being Effected" supplement, submitted under 21 CFR 314.70(c)(2), which provides for revisions to the PRECAUTIONS section of the package insert.

Review

The FPL package insert, identified as and was compared to the labeling submitted July 10, 1997 and the revisions requested in the August 28, 1997 approvable letter. (NOTE: The firm informed the Agency in a July 10, 1997 amendment, that the revised labeling contained in the amendment deletes all revisions previously proposed to the DOSAGE AND ADMINISTRATION, "Initial Dosage", "Laboratory Controls" and the "Conversion From Heparin Therapy" subsections). The editorial changes in the PHARMACOLOGY section, the "Clinical Trials" subsection, the "Myocardial Infarction" sub-subsection and the PRECAUTIONS section, the "Pediatric Use" subsection, and the description of the clinical trial for prophylaxis and/or treatment of deep vein thrombosis and pulmonary embolism were retained (see CSO labeling review date November 22, 1997). The package inserts are identical except for the following:

1. The identification codes were changed.

This change is ACCEPTABLE.
2. In the CLINICAL PHARMACOLOGY section (b)(4)

3. Supplement 090 provides for the following revisions to the PRECAUTIONS section:
   
a. In the list of ENDOGENOUS FACTORS (b)(4)

   b. In the list of ENDOGENOUS FACTORS that potentiates drug interactions with COUMADIN, the following was added to the "Specific Drugs Reported:

   (b)(4)

   
   c. In the "Special Risk Patients" subsection (b)(4)

   This addition should be reviewed by the MEDICAL OFFICER.

4. In the DOSAGE AND ADMINISTRATION section:
   
a. In the "Venous Thromboembolism (including pulmonary embolism)" subsection, the following sentences were added:

   This addition, as requested in the August 28, 1997 letter, is ACCEPTABLE.
b. In an August 27, 1997 letter to the firm, the Agency requested that the sponsor revise the labeling to clarify that additional PT tests are recommended only when the patient receives warfarin products that are not bioequivalent and therapeutically equivalent to Coumadin. Specifically, in "Laboratory Control" subsection, the last sentence in the first paragraph of the subsection should be revised from

request in an approvable letter.

Not initiating the requested changed is UNACCEPTABLE.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2., and 4.a.

2. The following changes should be reviewed by the MEDICAL OFFICER: 3.a.-c.

3. The following is UNACCEPTABLE: 4.b.

3. An approvable letter should be issued, re-iterating the request for revisions to the DOSAGE AND ADMINISTRATION section, the "Laboratory Control" subsection.

cc: Original 09-218/S-086 & S-090
    HFD-180/Div. Files
    HFD-180/K.Oliver
    HFD-180/L.Talarico
    HFD-180/K.Sizer
    HFD-180/M.Ysern
draft: KO/January 5, 1998
final: KO/05/18/98/c:\mydocuments\NDA092188-01-S86&90labbrev

CSO REVIEW
Re: NDA 9-218
Coumadin (warfarin sodium tablets, USP) Crystalline
MACMIS File ID#5702

Dear Mr. Abrams:

This correspondence is being submitted prior to the scheduled meeting of February 18, 1998 between representatives of The DuPont Merck Pharmaceutical Company ("DuPont Merck") and the Food and Drug Administration ("FDA").

First, we would like to emphasize that DuPont Merck has respect for the FDA’s approval process for reviewing and approving generic drugs and the reliability of the system for rating the therapeutic equivalence of generic drugs to innovator products. While we understand the concerns that the FDA has raised about the labeling of Coumadin® and the statements that the company has made based on that labeling, we hope that you recognize that we have always promoted our product consistent with our good faith understanding of the meaning of our FDA approved labeling.

Nevertheless, we agree to change labeling in accordance with the FDA’s recommendation specified in your letter of August 26, 1997. Specifically, the current statement:
In addition, as you know, we have previously reported to FDA several cases of patients who took both Coumadin® and Barr Laboratories' warfarin product simultaneously, which resulted in INR's far in excess of the therapeutic range. One of these patients experienced severe hemorrhage and a myocardial infarction. With the aim of preventing additional patients from inadvertently doubling their dosage, we also wish to add the following statement to the “Precautions” section of the Coumadin® package insert.

We no longer feel that the meeting DuPont Merck requested with the FDA is necessary. Instead we propose to submit the labeling changes to the Division of Gastrointestinal and Coagulation Drug Products and, if necessary, schedule a teleconference with the Division to discuss the proposals. We will call Tom Abrams one week prior to the scheduled meeting to confirm that FDA agrees that the scheduled meeting is no longer necessary.

Sincerely,

Richard S. Levy, M.D.
Vice President, Worldwide Regulatory Affairs
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA No. 9-218; Coumadin® Tablets (Warfarin Sodium Tablets, USP) Crystalline Coumadin® for Injection (Warfarin Sodium for Injection, USP)
Submission of Final Printed Labeling (Package Insert No. 6193 -18)
Amendment to Supplement Nos. S-086, S-090 and S-091

Dear Sir or Madam:

Reference is made to the teleconference held with Ms. Karen Oliver on May 18, 1998 regarding the use of two different dimensional and item numbers of the same Coumadin package insert. Use of two different dimensional and item numbers are necessary to accommodate packaging production lines of the various Coumadin put-ups.

In our May 7, 1998 labeling submission, we provided you with Final Printed labeling (Coumadin Package Insert No. 6466 -01). This package insert is used for the packaging of bottles of 1000 and Hospital Unit Dose Blister packages of 100.

Enclosed with this submission, we are providing you with 20 copies of Final Printed Labeling corresponding to Coumadin Package Insert No. 6193-18 for each of the following supplements: S-086, S-090 and S-091. This package insert represents the same text as the Coumadin package insert submitted with the labeling supplement dated May 7, 1998. This package insert will be used for the packaging of bottles of 100 and Coumadin for Injection.

We appreciate the Agency’s assistance in reviewing and approving the Coumadin Final printed labeling (Package inserts Nos. 6466-01 and 6193-18).

Sincerely,

Maida S. Burkha
Director, Regulatory Affairs
Phone: (302) 892-1873
Fax: (302) 892-0712
NDA 09-218

DuPont Merck Pharmaceutical Company
Attention: Mr. William R. Woolever
DuPont Merck Plaza, MR 2152
Wilmington, Delaware 19880-0721

JAN 1 2 1998

Dear Mr. Woolever:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coumadin® (Warfarin Sodium Tablets, USP) Tablets and Coumadin® (Warfarin Sodium for Injection, USP) for Injection.

The Agency has received more than 30 spontaneous safety reports describing patients who have developed epidural or spinal hematomas associated with the use of the low molecular weight heparin, Lovenox® (enoxaparin sodium) Injection, and spinal/epidural anesthesia or spinal puncture. Many of the hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Since these adverse events would be expected to occur if drugs with similar pharmacological activity were used in the same manner, the Agency issued a Health Advisory on December 11, 1997, to notify healthcare practitioners of important safety information related to these adverse events and that the manufacturers of low molecular weight heparins and heparinoids were requested to revise their package inserts to include additional safety information including a boxed warning.

The Agency is also aware of spontaneous safety reports and reports in published literature of epidural or spinal hematomas associated with the use of other anticoagulants, such as warfarin sodium and heparin sodium.

In order to receive further input on this issue, a meeting of the Anesthetic and Life Support Drugs Advisory Committee has been scheduled for February 5, 1998.
Because the preponderance of recent reports involves Lovenox® Injection, the Agency’s initial action concerns low molecular weight heparins and heparinoids. The advisory committee meeting has been organized accordingly. However, we wish to invite you to address the committee, in the public forum session, on the possible extension of the class warning to heparin sodium and warfarin sodium. Several options are available to you: (1) a brief, individual statement; (2) a joint statement with other heparin sodium or warfarin sodium manufacturers; or, (3) a written statement that will be read at the meeting.

If you wish to exercise one of the options listed above, or if you have any questions, please contact Karen Somers, Advisors and Consultants Staff, at (301) 443-5455.

For your convenience, a copy of the Federal Register notice announcing the date, time, location, and topic for the meeting and the December 11, 1997 Health Advisory are enclosed.

Sincerely yours,

[Signed]

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: (2)
cc:
Original NDA 09-218
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-021/K.Somers

Drafted by: B.Collier & K.Oliver/January 12, 1998
Initialed by: L.Talarico 01/13/98
final: KO/01/13/98/c:\wpfiles\karen\nda\09218801.2ko

GENERAL CORRESPONDENCE
FDA PUBLIC HEALTH ADVISORY

Subject: Reports of epidural or spinal hematomas with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture

Dear Health Care Professional:

The Food and Drug Administration (FDA) would like to call to your attention recent post marketing reports of patients who have developed epidural or spinal hematomas with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. Many of the hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. However, given the potential seriousness of this complication, we believe that patients and health care professionals should be notified of this information.

The postmarketing reports received to date involved patients who were treated with Lovenox, (enoxaparin sodium) Injection. However, the adverse event would be expected to occur drugs with similar pharmacological activity were used in the same manner. Therefore, the FDA has asked all manufacturers of low molecular weight heparins and heparinoids to revise their package inserts to provide further information for the safe and effective use of these drugs. Specifically, the manufacturers have been asked to include additional safety information and recommendations in a boxed warning in their package inserts.

SUMMARY OF REPORTS

- As of November, 1997, there have been more than 30 spontaneous safety reports describing patients who have developed epidural or spinal hematomas with concurrent use of enoxaparin sodium and spinal/epidural anesthesia or spinal puncture. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

- Approximately 75% of the patients were elderly women undergoing orthopedic surgery.

At this time, the FDA believes practitioners should be aware of the following points if using these products:

- When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

- The risk of these events is increased by the use of indwelling epidural catheters for


1/13/98
administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

- Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.
- Practitioners should consider fully the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

The FDA will continue to monitor closely post marketing reports for additional events. We encourage all health care professionals to report any serious adverse events, including cases of epidural or spinal hematomas, occurring with the use of low molecular weight heparins, heparinoids, or other anticoagulant to the FDA's MEDWATCH program at 1-800-FDA-1088/fax 1-800-FDA-0178; or to the respective pharmaceutical manufacturers:

- Fragmin (dalteparin sodium injection); Pharmacia & Upjohn; 1-800-253-8600, ext. 38244.
- Lovenox (enoxaparin sodium) Injection; Rhone-Poulenc Rorer Pharmaceuticals Inc.; 1-800-340-7502.
- Normiflo (ardeparin sodium) Injection; Wyeth Laboratories Inc.; 1-800-934-5556.
- Orgaran (danaparoid sodium) Injection; Organon Inc.; 1-800-631-1253.

Sincerely yours,

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

Return to Summary


1/13/98
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 9-218
Drug: Coumadin® (Warfarin Sodium)
Sponsor: DuPont Merck
Subj: Resubmission of Final Printed Labeling
Date: March 20, 1998
Reviewer: Kurt Sizer, M.D.

I. Background

Warfarin is currently indicated for the prophylaxis and treatment of venous thrombosis and pulmonary embolism, and for prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and cardiac valve replacement. Warfarin is also recommended for the reduction of the risk of death, recurrent myocardial infarction, and thromboembolic complications such as stroke, or systemic embolization following a myocardial infarction.

The most recent Labeling Supplement for Coumadin® (S-086) was reviewed in MOR 2/25/97. Three amendments to this supplement were subsequently submitted and approved on draft. Subsequent revisions to the final printed labeling were reviewed in MOR 2/6/98, and additional proposed revisions have now been submitted for review.

II. Proposed changes to the Professional Label

A. Two additions to the professional label were proposed to the professional label, based on the recent report by Warkentin TE et. al. (Ann Intern Med 1997;11:804), who retrospectively identified 8 patients over a 15-year period, with Type II Heparin-induced thrombocytopenia (HIT) and deep venous thrombosis, who developed venous limb gangrene with the use of warfarin. Large initial doses of warfarin were associated with the development of this complication; likely due to the rapid and significant depletion of Protein C in the setting of a HIT-associated prothrombotic state. The Agency brought this study to the attention of the sponsor, who has now proposed two additions to the professional label for Coumadin®.
cc:
NDA 9-218
HFD-180
HFD-180/LTalaric
HFD-180/KSizer
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/c 3/20/98 jgw
MED\N\9218803.0KS

/S/ 3/21/98
Kurt Sizer, M.D.
April 22, 1998

Sent Via Facsimile

Ms. Karen Oliver
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 9-218
Coumadin® Tablets (Warfarin Sodium Tablets, USP) Crystalline
General Correspondence

Dear Karen:

Thank you for returning my call this morning to discuss the letter sent by the Agency on April 16, 1998.

As agreed, we will submit a Changes Being Effected supplemental application to include all the changes in the labeling that we have accepted from the Agency that are not covered in previously submitted supplements (S-086 and S-090). We will also submit the Final Printed Labeling that will be filed with the Changes Being Effected supplemental application as revised Final Printed Labeling to supplements S-086 and S-090.

Since we are currently in the process of including all the changes as indicated in the April 16, 1998 letter from the Agency, I want to bring to your attention three minor changes.

1) The letter from the Agency did not indicate acceptance or objection to the revision to the third paragraph of WARNINGS

This change will be included in the Final Printed labeling and will be noted in the Changes Being Effected supplemental application.
2) The Agency commented on the need to:

The Final Printed labeling will read as indicated:

3) The realignment of numbers in CLINICAL PHARMACOLOGY occurred in Table 2 of CLINICAL PHARMACOLOGY Section. The letter from the Agency listed it as Table 4.

I would very much appreciate it if you were to call me today so that we can obtain your concurrence.

Sincerely,

Maada Burka
DuPont Merck Pharmaceutical Company
Director Regulatory Affairs
Telephone: (302) 892-1873
Facsimile: (302) 892-0712
May 7, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)
Document Control Room 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA No. 9-218: Coumadin® Tablets (Warfarin Sodium Tablets, USP) Crystalline
Coumadin® for Injection (Warfarin Sodium for Injection, USP)
Submission of New Changes Being Effected Supplement
Amendment to Supplement Nos. S-086 and S-090
Submission of Final Printed Labeling

Dear Sir or Madam:

Reference is made to the April 16, 1998, letter from the Agency, which provided recommendations
to proposed labeling changes submitted by DuPont Merck on March 3, 1998. Reference is also made
to the April 22, 1998, telephone conversation between Ms. Maida Burka, of DuPont Merck and
Ms. Karen Oliver to discuss these proposed labeling changes and the Agency's recommendations.
Subsequent to this discussion, other contacts were made with the Agency to gain further
clarification on the recommended changes.

In response to these discussions, we enclose 20 copies of Final Printed Labeling for each
supplement. This Final Printed Labeling includes the changes recommended by the Agency for
supplements S-086, S-090 and the New Changes Being Effected supplement submitted with this
letter.

As agreed upon with Dr. Talarico on April 30, an additional modification has been made and is
incorporated into the enclosed Final Printed Labeling. The following sentence under the
Information for Patients subsection has been bolded:
To assist in your review, also enclosed are:

- a summary index, which outlines each of the modifications and the corresponding supplement to which each change applies; and
- an annotated package insert reflecting the changes corresponding to supplements S-086, S-090 and the New Changes Being Effected supplement.

We appreciate the Agency's assistance in the rapid review and approval of these labeling changes.

Sincerely,

[Signature]

Maida S. Burk
Director of Regulatory Affairs
Telephone: (302) 892-1873
Facsimile: (302) 892-0712

Submitted in Duplicate
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 09-218

Name of Drug: Coumadin® (Warfarin Sodium Tablets, USP) Tablets
Coumadin® (Warfarin Sodium for Injection, USP) for Injection

Sponsor: The DuPont Merck Pharmaceutical Company

Material Reviewed

Submission Date(s): March 3, 1998

Receipt Date(s): March 4, 1998

Background and Summary Description: The firm submitted proposed labeling changes for Coumadin, cross-referencing to previous submission (S-086 and S-090) currently under review and to supportive documentation of addition labeling changes to be submitted in a "Special Supplement-Changes Being Effected" (CBE) supplement.

Review

The proposed draft package insert, identified as "DATE PREPARED: February, 1998" was compared to the labeling approved November 18, 1996 in supplement 083, identified as "6386-04/Rev.August, 1996". The package insert was identical except for the following:

1. The identification codes were changed.

   This change is ACCEPTABLE.

2. In the CLINICAL PHARMACOLOGY section, the "Clinical Trials" subsection:

   a. In the "Atrial Fibrillation (AF)" sub-subsection, in the first sentence of the subsection

   This change is ACCEPTABLE.

   b. In the "Myocardial Infarction" sub-subsection:

   (1) In the second sentence, the phrase
This change is ACCEPTABLE.

(2) In Table 2

This change is ACCEPTABLE.

c. In the "Mechanical and Bioprosthetic Heart Valves" sub-subsection:

(1) In the last sentence of the third paragraph

This change is ACCEPTABLE.

(2) In the first sentence of the third paragraph

This change is ACCEPTABLE.

3. In the WARNINGS section:

a. In the third paragraph, the underlined words were changed

This change is ACCEPTABLE per Dr. Lilia Talarico, Division Director.

b. A new paragraph was added as the seventh paragraph of the section to read:
This addition is UNACCEPTABLE (see the March 23, 1998, Medical Officer's Review). The paragraph should be revised

c. In the "Lactation" subsection

This change is ACCEPTABLE.

4. In the PRECAUTIONS section:

a. In the EXOGENOUS FACTORS section (increased PT/INR response), in the "Classes of Drugs" list

These additions are UNACCEPTABLE as they are incomplete. The drug classes for the specific drugs
b. In the "Special Risk Patients" subsection

- This addition is UNACCEPTABLE (see the February 9, 1998 Medical Officer's Review).

c. In the "Information to Patients" subsection,

5. In the DOSAGE AND ADMINISTRATION section:

a. In the "Venous Thromboembolism (including pulmonary embolism)" subsection
This addition is ACCEPTABLE (see the July 22, 1997 Medical Officer’s Review).

b. In the "Post-Myocardial Infarction" section

This addition is ACCEPTABLE.

c. In the "Laboratory Controls" subsection

6. After the HOW SUPPLIED section

This change is ACCEPTABLE.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2.a., 2.b.(1)-(2), 2.c.(1)-(2), 3.a., 3.c., 5.a.-b., and 6.

2. The following changes are UNACCEPTABLE: 3.b., 4.a.-c., and 5.c.

/S/

Karen Oliver
Regulatory Health Project Manager
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 09-218/S-086, 090, and 091

Name of Drug: Coumadin® (Warfarin Sodium Tablets, USP) Tablets
Coumadin® (Warfarin Sodium for Injection, USP) for Injection

Sponsor: The DuPont Merck Pharmaceutical Company

Material Reviewed

Submission Date(s): May 7, 1998 (FPL "64660-01/Rev.April, 1998")
     May 20, 1998 (FPL "6193-18/Rev.April, 1998")

Receipt Date(s): May 8, 1998 (FPL "64660-01/Rev.April, 1998")
     May 21, 1998 (FPL "6193-18/Rev.April, 1998")

Background and Summary Description: The firm submitted final printed labeling (FPL) for the following "Special Supplement-Changes Being Effected" (CBE) supplements: S-086 (submitted August 16, 1996), S-090 (submitted December 31, 1997) and S-091 (submitted May 7, 1998).

Review

Each of the two versions of the submitted FPL for the three supplements, identified as "64660-01/Rev.April, 1998" and "6193-18/Rev.April, 1998", was compared to the labeling approved November 18, 1996 in supplement 083, identified as "6386-04/Rev.August, 1996" and "6193-17/Rev.Aug., 1996". The package inserts were identical except for the following:

1. The paper weight of the package inserts has increased.

   This change is ACCEPTABLE.

2. The identification numbers changed.

   This change is ACCEPTABLE.
3. In the CLINICAL PHARMACOLOGY section, the "Clinical Trials" subsection:

   a. In S-090, in the "Atrial Fibrillation (AF)" sub-subsection

      This change is ACCEPTABLE (see the April 16, 1998 Consumer Safety Review and the April 16, 1998 Agency letter to the firm).

   b. In the "Myocardial Infarction" sub-subsection:

   c. In the "Mechanical and Bioprosthetic Heart Valves" sub-subsection:
4. In the WARNINGS section:

This addition is ACCEPTABLE (see the March 23, 1998 Medical Officer Review, the April 16, 1998 Consumer Safety Officer Review, and the April 16, 1998 Agency letter to the firm).

c. In S-090, in the "Lactation" subsection,
5. In the PRECAUTIONS section:

6. In the DOSAGE AND ADMINISTRATION section:
b. In S-090, in the "Post-Myocardial Infarction" subsection

c. In the "Laboratory Controls" subsection:

7. In S-091, after the HOW SUPPLIED section
Conclusions

Each of the two versions of FPL package submitted for the three supplements (086, 090, and 091) are ACCEPTABLE.

/S/  \[Signature\]
Karen Oliver, RN, MSN
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

6-1-98