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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 09218/S086/S090/S091

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)				X
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 09218/S086/S090/S091

APPROVAL LETTER

NDA 09-218/S-086
NDA 09-218/S-090
NDA 09-218/S-091

JUN - 1 1998

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,

/S/ 6-1-98

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

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)
HFI-20/Press Office (with labeling)

APPEARS THIS WAY
ON ORIGINAL

Drafted by: KO/June 1, 1998 /S/ 06/01/98
final: KO/06/01/98/c:\mydocuments\NDA0921806-01-98-AP

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09218/S086/S090/S091

FINAL PRINTED LABELING

SUR/AF 95 SUR/AF 091

Labeling: Drug SUR/AF 600 SUR/AF 091

NDA No: 9218 Rec'd. 5/15/98

Reviewed by: KOlmer 5/6/98

Specific Drugs Reported		
acetaminophen	fluorouracil	penicillin G, intravenous
alcohol†	fluoxetine	pentoxifylline
allopurinol	flutamide	phenylbutazone
aminosalicylic acid	fluvoxamine	phenytoin†
amiodarone HCl	glucagon	piperacillin

A risk of hepatitis and other viral diseases is associated with the use of these blood products. Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to COUMADIN (Warfarin Sodium) overdosage.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of COUMADIN treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating

6193-18/Rev. April, 1998

COUMADIN® TABLETS

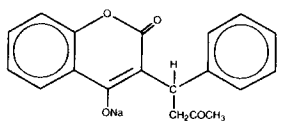
Anticoagulant **(Warfarin Sodium Tablets, USP) Crystalline**

COUMADIN® FOR INJECTION

(Warfarin Sodium for Injection, USP)

DESCRIPTION

COUMADIN (crystalline warfarin sodium), is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is $C_{19}H_{15}NaO_4$ and its structural formula may be represented by the following:



APPROVED

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

COUMADIN Tablets for oral use also contain:

All strengths:	Lactose, starch and magnesium stearate
1 mg:	D&C Red No. 6 Barium Lake
2 mg:	FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
2-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
3 mg:	FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
4 mg:	FD&C Blue No. 1 Aluminum Lake
5 mg:	FD&C Yellow No. 6 Aluminum Lake
6 mg:	FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
7-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake
10 mg:	Dye Free

COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection, contains:

Warfarin Sodium	2 mg/mL
Sodium Phosphate, Dibasic, Heptahydrate	4.98 mg/mL
Sodium Phosphate, Monobasic, Monohydrate	0.194 mg/mL
Sodium Chloride	0.1 mg/mL
Mannitol	38.0 mg/mL
Sodium Hydroxide, as needed for pH adjustment to	8.1 to 8.3

CLINICAL PHARMACOLOGY

COUMADIN and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4-6 hours, IX - 24 hours, and X - 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

Pharmacokinetics: COUMADIN is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption: *COUMADIN is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.*

Distribution: There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see WARNINGS - Lactation). Approximately 99% of the drug is bound to plasma proteins.

INDICATIONS AND USAGE

COUMADIN (Warfarin Sodium) is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

COUMADIN is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

COUMADIN is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

CONTRAINDICATIONS

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

Pregnancy: COUMADIN is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus *in utero*. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following *in utero* exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and still birth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation.

Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS

The most serious risks associated with anticoagulant therapy with sodium warfarin are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. COUMADIN, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and COUMADIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Caution should be observed when COUMADIN is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis, and/or gangrene is present.

Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction.

COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection, contains:

Warfarin Sodium	2 mg/mL
Sodium Phosphate, Dibasic, Heptahydrate	4.98 mg/mL
Sodium Phosphate, Monobasic, Monohydrate	0.194 mg/mL
Sodium Chloride	0.1 mg/mL
Mannitol	38.0 mg/mL
Sodium Hydroxide, as needed for pH adjustment to	8.1 to 8.3

CLINICAL PHARMACOLOGY

COUMADIN and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4-6 hours, IX - 24 hours, and X - 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

Pharmacokinetics: COUMADIN is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption: *COUMADIN is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.*

Distribution: There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see WARNINGS - Lactation). Approximately 99% of the drug is bound to plasma proteins.

Metabolism: The elimination of warfarin is almost entirely by metabolism. COUMADIN is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4'-, 6-, 7-, 8- and 10-hydroxywarfarin. The Cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion: The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Elderly: There are no significant age-related differences in the pharmacokinetics of racemic warfarin. Limited information suggests that there is no difference in the clearance of S-warfarin in elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly compared to the young. Older patients (60 years or older) appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. As patient age increases, less warfarin is required to produce a therapeutic level of anticoagulation. The cause of this response to warfarin is not known.

Renal Dysfunction: Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic Dysfunction: Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of COUMADIN via the intravenous (I.V.) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin may not be achieved until 72-96 hours after dosing, indicating that the administration of I.V. COUMADIN should not provide any increased biological effect or earlier onset of action.

Clinical Trials

Atrial Fibrillation (AF): In five prospective randomized controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (See Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (See Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.

TABLE 1
CLINICAL STUDIES OF WARFARIN IN NON-RHEUMATIC AF PATIENTS*

Study	N		PT Ratio	INR	Thromboembolism		% Major Bleeding	
	Warfarin-Treated Patients	Control Patients			%Risk Reduction	*p*-value	Warfarin-Treated Patients	Control Patients
AFASAK	335	336	1.5-2.0	2.8-4.2	60	0.027	0.6	0.0
SPAF	210	211	1.3-1.8	2.0-4.5	67	0.01	1.9	1.9

dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation.

Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS

The most serious risks associated with anticoagulant therapy with sodium warfarin are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. COUMADIN, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and COUMADIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Caution should be observed when COUMADIN is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis, and/or gangrene is present.

Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3-10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time. While the purple toes syndrome is reported to be reversible, some cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.

Heparin-induced thrombocytopenia: COUMADIN 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).

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

Lactation: COUMADIN appears in the milk of nursing mothers in an inactive form. Infants nursed by mothers treated with COUMADIN had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.

Severe to moderate hepatic or renal insufficiency.

Infectious diseases or disturbances of intestinal flora: sprue, antibiotic therapy.

Trauma which may result in internal bleeding.

Surgery or trauma resulting in large exposed raw surfaces.

Indwelling catheters.

Severe to moderate hypertension.

Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Miscellaneous: polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to COUMADIN have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly compared to the young. Older patients (60 years or older) appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. As patient age increases, less warfarin is required to produce a therapeutic level of anticoagulation. The cause of this response to warfarin is not known.

Renal Dysfunction: Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic Dysfunction: Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of COUMADIN via the intravenous (I.V.) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin may not be achieved until 72-96 hours after dosing, indicating that the administration of I.V. COUMADIN should not provide any increased biological effect or earlier onset of action.

Clinical Trials

Atrial Fibrillation (AF): In five prospective randomized controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (See Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (See Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.

TABLE 1
CLINICAL STUDIES OF WARFARIN IN NON-RHEUMATIC AF PATIENTS*

Study	N		PT Ratio	INR	Thromboembolism		% Major Bleeding	
	Warfarin-Treated Patients	Control Patients			%Risk Reduction	*p*-value	Warfarin-Treated Patients	Control Patients
AFASAK	335	336	1.5-2.0	2.8-4.2	60	0.027	0.6	0.0
SPAF	210	211	1.3-1.8	2.0-4.5	67	0.01	1.9	1.9
BAATAF	212	208	1.2-1.5	1.5-2.7	86	<0.05	0.9	0.5
CAFA	187	191	1.3-1.6	2.0-3.0	45	0.25	2.7	0.5
SPINAF	260	265	1.2-1.5	1.4-2.8	79	0.001	2.3	1.5

*All study results of warfarin vs. control are based on intention-to-treat analysis and include ischemic stroke and systemic thromboembolism, excluding hemorrhage and transient ischemic attacks.

Myocardial Infarction: WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. [But note that a lower INR was achieved and increased bleeding was associated with INR's above 4.0; (see DOSAGE AND ADMINISTRATION)]. The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table:

TABLE 2

Event	Warfarin (N=607)	Placebo (N=607)	RR (95%CI)	% Risk Reduction (p-value)
Total Patient Years of Follow-up	2018	1944		
Total Mortality	94 (4.7/100 py)	123 (6.3/100 py)	0.76 (0.60, 0.97)	24 (p=0.030)
Vascular Death	82 (4.1/100 py)	105 (5.4/100 py)	0.78 (0.60, 1.02)	22 (p=0.068)
Recurrent MI	82 (4.1/100 py)	124 (6.4/100 py)	0.66 (0.51, 0.85)	34 (p=0.001)
Cerebrovascular Event	20 (1.0/100 py)	44 (2.3/100 py)	0.46 (0.28, 0.75)	54 (p=0.002)

RR=Relative risk; Risk reduction=(1 - RR); CI=Confidence interval; MI=Myocardial infarction; py=patient years

Mechanical and Bioprosthetic Heart Valves: In a prospective, randomized, open label, positive-controlled study (Mok et al, 1985) in 254 patients, the thromboembolic-free interval was found to be significantly greater in patients with mechanical prosthetic heart valves treated with warfarin alone compared with dipyridamole-aspirin ($p<0.005$) and pentoxifylline-aspirin ($p<0.05$) treated patients. Rates of thromboembolic events in these groups were 2.2, 8.6, and 7.9/100 patient years, respectively. Major bleeding rates were 2.5, 0.0, and 0.9/100 patient years, respectively.

In a prospective, open label, clinical trial (Saour et al, 1990) comparing moderate (INR 2.65) vs. high intensity (INR 9.0) warfarin therapies in 258 patients with mechanical prosthetic heart valves, thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events/100 patient years, respectively). Major bleeding was more common in the high intensity group (2.1 events/100 patient years) vs. 0.95 events/100 patient years in the moderate intensity group.

In a randomized trial (Turpie et al, 1988) in 210 patients comparing two intensities of warfarin therapy (INR 2.0-2.25 vs. INR 2.5-4.0) for a three-month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (major hemorrhages 4.6%) vs. none in the lower intensity.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

Lactation: COUMADIN appears in the milk of nursing mothers in an inactive form. Infants nursed by mothers treated with COUMADIN had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.

Severe to moderate hepatic or renal insufficiency.

Infectious diseases or disturbances of intestinal flora: sprue, antibiotic therapy.

Trauma which may result in internal bleeding.

Surgery or trauma resulting in large exposed raw surfaces.

Indwelling catheters.

Severe to moderate hypertension.

Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Miscellaneous: polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to COUMADIN have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

PRECAUTIONS

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with COUMADIN through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with COUMADIN are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with COUMADIN are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

ENDOGENOUS FACTORS:

blood dyscrasias - see CONTRAINDICATIONS	hepatic disorders
cancer	infectious hepatitis
collagen vascular disease	jaundice
congestive heart failure	hyperthyroidism
diarrhea	poor nutritional state
elevated temperature	steatorrhea
	vitamin K deficiency

EXOGENOUS FACTORS:

Potential drug interactions with COUMADIN are listed below by drug class and by specific drugs.

Classes of Drugs		
5-lipoxygenase Inhibitor	Antimalarial Agents	Hypnotics†
Adrenergic Stimulants, Central	Antineoplastics†	Hypolipidemics†
Alcohol Abuse Reduction Preparations	Antiparasitic/Antimicrobials	Leukotriene Receptor Antagonist
Analgesics	Antiplatelet Drugs/Effects	Monoamine Oxidase Inhibitors
Anesthetics, Inhalation	Antithyroid Drugs†	Narcotics, prolonged
Antiandrogen	Beta-Adrenergic Blockers	Nonsteroidal Anti-Inflammatory Agents
Antiarrhythmics†	Bromelains	Psychostimulants
Antibiotics†	Cholelitholytic Agents	Pyrazolones
Aminoglycosides (oral)	Diabetes Agents, Oral	Salicylates
Cephalosporins, parenteral	Diuretics†	Selective Serotonin Reuptake Inhibitors
Macrolides	Fungal Medications, Systemic†	Steroids, Adrenocortical†
Miscellaneous	Gastric Acidity and Peptic Ulcer Agents†	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Penicillins, intravenous, high dose	Gastrointestinal, Ulcerative Colitis Agents	Thrombolytics
Quinolones (fluoroquinolones)	Gout Treatment Agents	Thyroid Drugs
Sulfonamides, long acting	Hemorrheologic Agents	Tuberculosis Agents†
Tetracyclines	Hepatotoxic Drugs	Uricosuric Agents
Anticoagulants	Hyperglycemic Agents	Vaccines
Anticonvulsants†	Hypertensive Emergency Agents	Vitamins†
Antidepressants†		

Specific Drugs Reported		
acetaminophen	fluorouracil	penicillin G, intravenous
alcohol†	fluoxetine	pentoxifylline
allopurinol	flutamide	phenylbutazone
aminosalicylic acid	fluvoxamine	phenytoin†
amiodarone HCl	glucagon	piperacillin
aspirin	halothane	piroxicam
azithromycin	heparin	prednisone†
cefamandole	ibuprofen	propafenone
cefazolin	ifosfamide	propoxyphene
cefoperazone	indomethacin	propranolol
cefotetan	influenza virus vaccine	propylthiouracil†
cefoxitin	itraconazole	quinidine
ceftriaxone	ketoprofen	quinine
chenodiol	ketorolac	ranitidine†
chloramphenicol	levamisole	sertraline
chloral hydrate†	levothyroxine	simvastatin
chlorpropamide	liothyronine	stanozolol
cholestyramine†	lovastatin	streptokinase
cimetidine	mefenamic acid	sulfamethizole
ciprofloxacin	methimazole†	sulfamethoxazole
clarithromycin	methyldopa	sulfinpyrazone
clofibrate	methylphenidate	sulfisoxazole
COUMADIN overdose	methylsalicylate ointment (topical)	sulindac
cyclophosphamide†	metronidazole	tamoxifen
danazol	miconazole	tetracycline
dextran	moricizine hydrochloride†	thyroid
dextrothyroxine	nalidixic acid	ticarcillin
diazoxide	naproxen	ticlopidine
diclofenac	neomycin	tissue plasminogen activator (t-PA)
dicumarol	norfloxacin	tolbutamide
diflunisal	ofloxacin	trimethoprim/sulfamethoxazole
disulfiram	olsalazine	urokinase
doxycycline	omeprazole	valproate
erythromycin	oxaprozin	vitamin E
ethacrynic acid	oxymetholone	zafirlukast
fenoprofen	paroxetine	zileuton
fluconazole		

also: other medications affecting blood elements which may modify hemostasis
dietary deficiencies
prolonged hot weather
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

ENDOGENOUS FACTORS:

edema	hypothyroidism
hereditary coumarin resistance	nephrotic syndrome
hyperlipemia	

EXOGENOUS FACTORS:
Potential drug interactions with COUMADIN (Warfarin Sodium) are listed below by drug class and by specific drugs.

Classes of Drugs		
Adrenal Cortical Steroid Inhibitors	Antipsychotic Medications	Hypnotics†
Antacids	Antithyroid Drugs†	Hypolipidemics†
Antianxiety Agents	Barbiturates	Immunosuppressives
Antiarrhythmics†	Diuretics†	Oral Contraceptives, Estrogen Containing
Antibiotics†	Enteral Nutritional Supplements	Steroids, Adrenocortical†
Anticonvulsants†	Fungal Medications, Systemic†	Tuberculosis Agents†
Antidepressants†	Gastric Acidity and Peptic Ulcer Agents†	Vitamins†
Antihistamines		
Antineoplastics†		

Specific Drugs Reported		
alcohol†	COUMADIN underdosage	phenobarbital
aminoglutethimide	cyclophosphamide†	phenytoin†
amobarbital	dicloxacillin	prednisone†
azathioprine	ethchlorvynol	primidone
butabarbital	glutethimide	propylthiouracil†
butalbital	griseofulvin	ranitidine†
carbamazepine	haloperidol	rifampin
chloral hydrate†	meprobamate	secobarbital
chlordiazepoxide	6-mercaptopurine	spironolactone
chlorthalidone	methimazole†	sucralfate
cholestyramine†	moricizine hydrochloride†	trazodone
corticotropin	nafcillin	vitamin C (high dose)
cortisone	paraldehyde	vitamin K
	pentobarbital	

also: diet high in vitamin K
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of COUMADIN on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these

A risk of hepatitis and other viral diseases is associated with the use of these blood products; Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to COUMADIN (Warfarin Sodium) overdosage.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of COUMADIN treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSAGE AND ADMINISTRATION

The dosage and administration of COUMADIN must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See LABORATORY CONTROL below for full discussion on INR.)

Venous Thromboembolism (including pulmonary embolism): Available clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs. 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).

Atrial Fibrillation: Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients.

Post-Myocardial Infarction: In post-myocardial infarction patients, COUMADIN therapy should be initiated early (2-4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5-3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of COUMADIN therapy at the lower end of this INR range is recommended.

Mechanical and Bioprosthetic Heart Valves: In patients with mechanical heart valve(s), long term prophylaxis with warfarin to an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

Recurrent Systemic Embolism: In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage: The dosing of COUMADIN must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Low initiation doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to COUMADIN (see PRECAUTIONS). It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of Therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose: The anticoagulant effect of COUMADIN persists beyond 24 hours. If the patient forgets to take the prescribed dose of COUMADIN at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Intravenous Route of Administration: COUMADIN for Injection provides an alternate administration route for patients who cannot receive oral drugs. The I.V. dosages would be the same as those that would be used orally if the patient could take the drug by the oral route. COUMADIN for Injection should be administered as a slow bolus injection over 1 to 2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be reconstituted with 2.7 mL of sterile Water for Injection and inspected for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted. After reconstitution, COUMADIN for Injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to assure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to COUMADIN in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, were used to perform the test. Early clinical

Antianxiety Agents Antiarrhythmics† Antibiotics† Anticonvulsants† Antidepressants† Antihistamines Antineoplastics†	Diuretics† Enteral Nutritional Supplements Fungal Medications, Systemic† Gastric Acidity and Peptic Ulcer Agents†	Oral Contraceptives Containing Steroids, Adrenocortical† Tuberculosis Agents† Vitamins†

Specific Drugs Reported		
alcohol†	COUMADIN underdosage	phenobarbital
aminoglutethimide	cyclophosphamide†	phenytoin†
amobarbital	dicloxacillin	prednisone†
azathioprine	ethchlorvynol	primidone
butabarbital	glutethimide	propylthiouracil†
butalbital	griseofulvin	ranitidine†
carbamazepine	haloperidol	rifampin
chloral hydrate†	meprobamate	secobarbital
chlordiazepoxide	6-mercaptopurine	spironolactone
chlorthalidone	methimazole†	sucralfate
cholestyramine†	moricizine hydrochloride†	trazodone
corticotropin	nafcillin	vitamin C (high dose)
cortisone	paraldehyde	vitamin K
	pentobarbital	

also: diet high in vitamin K
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of COUMADIN on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

Effect on Other Drugs: Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Special Risk Patients: COUMADIN is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when COUMADIN (or warfarin) is administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance should be suspected if large daily doses of COUMADIN are required to maintain a patient's PT/INR within a normal therapeutic range.

Information for Patients: The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics) and other over-the-counter medications except on advice of the physician. Avoid alcohol consumption. Do not take COUMADIN during pregnancy and do not become pregnant while taking it (see CONTRAINDICATIONS). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that COUMADIN is being taken. If the prescribed dose of COUMADIN is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of COUMADIN the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with COUMADIN. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with COUMADIN is discontinued, patients should be cautioned that the anticoagulant effects of COUMADIN may persist for about 2 to 5 days. **Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and mutagenicity studies have not been performed with COUMADIN. The reproductive effects of COUMADIN have not been evaluated.

Use in Pregnancy: Pregnancy Category X - See CONTRAINDICATIONS.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established, in randomized, controlled clinical trials. However, the use of COUMADIN in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

ADVERSE REACTIONS

Potential adverse reactions to COUMADIN may include:

- Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See OVERDOSAGE–Treatment.)

should be administered as a slow bolus injection over 1 to 2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be reconstituted with 2.7 mL of sterile Water for Injection and inspected for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted. After reconstitution, COUMADIN for Injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to assure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to COUMADIN in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, were used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: INR = (observed PT ratio) ^{ISI} where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[2-4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.[5]

TABLE 3
Relationship Between INR and PT Ratios
For Thromboplastins With Different ISI Values (Sensitivities)

	PT RATIOS				
	ISI 1.0	**ISI 1.4**	**ISI 1.8**	**ISI 2.3**	**ISI 2.8**
INR = 2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR = 2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

TREATMENT DURING DENTISTRY AND SURGERY The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of COUMADIN to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of COUMADIN therapy. When discontinuing COUMADIN even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of COUMADIN is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that COUMADIN therapy be overlapped with heparin for 4 to 5 days, until COUMADIN has produced the desired therapeutic response as determined by PT/INR. When COUMADIN has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

COUMADIN may increase the aPTT test, even in the absence of heparin. During initial therapy with COUMADIN, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and COUMADIN should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

Tablets: For oral use, single scored, imprinted numerically and packaged in bottles with potencies and colors as follows:

	30's	**100's**	**1000's**	**Hospital Unit-Dose blister package of 100**
1 mg pink		NDC 0056-0169-70	NDC 0056-0169-90	NDC 0056-0169-75
2 mg lavender	NDC 0056-0170-30	NDC 0056-0170-70	NDC 0056-0170-90	NDC 0056-0170-75
2-1/2 mg green	NDC 0056-0176-30	NDC 0056-0176-70	NDC 0056-0176-90	NDC 0056-0176-75
3 mg tan		NDC 0056-0188-70	NDC 0056-0188-90	NDC 0056-0188-75
4 mg blue		NDC 0056-0168-70	NDC 0056-0168-90	NDC 0056-0168-75
5 mg peach	NDC 0056-0172-30	NDC 0056-0172-70	NDC 0056-0172-90	NDC 0056-0172-75
6 mg teal		NDC 0056-0189-70	NDC 0056-0189-90	NDC 0056-0189-75
7-1/2 mg yellow		NDC 0056-0173-70		NDC 0056-0173-75
10 mg white (Dye Free)		NDC 0056-0174-70		NDC 0056-0174-75

decimated or when administered in any situation of physical condition where added risk of hemorrhage is present.

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when COUMADIN (or warfarin) is administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance should be suspected if large daily doses of COUMADIN are required to maintain a patient's PT/INR within a normal therapeutic range.

Information for Patients: The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics) and other over-the-counter medications except on advice of the physician. Avoid alcohol consumption. Do not take COUMADIN during pregnancy and do not become pregnant while taking it (see CONTRAINDICATIONS). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that COUMADIN is being taken. If the prescribed dose of COUMADIN is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of COUMADIN the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with COUMADIN. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with COUMADIN is discontinued, patients should be cautioned that the anticoagulant effects of COUMADIN may persist for about 2 to 5 days. **Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and mutagenicity studies have not been performed with COUMADIN. The reproductive effects of COUMADIN have not been evaluated.

Use in Pregnancy: Pregnancy Category X - See CONTRAINDICATIONS.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established, in randomized, controlled clinical trials. However, the use of COUMADIN in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

ADVERSE REACTIONS

Potential adverse reactions to COUMADIN may include:

- Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See OVERDOSAGE–Treatment.)
- Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.
- Necrosis of skin and other tissues. (See WARNINGS.)
- Adverse reactions reported infrequently include: hypersensitivity/allergic reactions, systemic cholesterol microembolization, 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.

Rare events of tracheal or tracheobronchial calcification have been reported in association with long-term warfarin therapy. The clinical significance of this event is unknown.

Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

OVERDOSAGE

Signs and Symptoms: Suspected or overt abnormal bleeding (e.g., appearance of blood in stools or urine, hematuria, excessive menstrual bleeding, melena, petechiae, excessive bruising or persistent oozing from superficial injuries) are early manifestations of anticoagulation beyond a safe and satisfactory level.

Treatment: Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing COUMADIN therapy and if necessary, by administration of oral or parenteral vitamin K_1. (Please see recommendations accompanying vitamin K_1 preparations prior to use.)

Such use of vitamin K_1 reduces response to subsequent COUMADIN therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of COUMADIN administration reverses the effect of vitamin K, and a therapeutic PT/INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

If minor bleeding progresses to major bleeding, give 5 to 25 mg (rarely up to 50 mg) parenteral vitamin K_1. In emergency situations of severe hemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of fresh whole blood or fresh frozen plasma, or by giving commercial Factor IX complex.

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[3] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.[5]

TABLE 3
Relationship Between INR and PT Ratios
For Thromboplastins With Different ISI Values (Sensitivities)

	PT RATIOS				
	ISI 1.0	**ISI 1.4**	**ISI 1.8**	**ISI 2.3**	**ISI 2.8**
INR = 2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR = 2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

TREATMENT DURING DENTISTRY AND SURGERY The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of COUMADIN to maintain the PT /INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of COUMADIN therapy. When discontinuing COUMADIN even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of COUMADIN is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that COUMADIN therapy be overlapped with heparin for 4 to 5 days, until COUMADIN has produced the desired therapeutic response as determined by PT/INR. When COUMADIN has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

COUMADIN may increase the aPTT test, even in the absence of heparin. During initial therapy with COUMADIN, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and COUMADIN should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

Tablets: For oral use, single scored, imprinted numerically and packaged in bottles with potencies and colors as follows:

	30's	**100's**	**1000's**	**Hospital Unit-Dose blister package of 100**
1 mg pink		NDC 0056-0169-70	NDC 0056-0169-90	NDC 0056-0169-75
2 mg lavender	NDC 0056-0170-30	NDC 0056-0170-70	NDC 0056-0170-90	NDC 0056-0170-75
2-1/2 mg green	NDC 0056-0176-30	NDC 0056-0176-70	NDC 0056-0176-90	NDC 0056-0176-75
3 mg tan		NDC 0056-0188-70	NDC 0056-0188-90	NDC 0056-0188-75
4 mg blue		NDC 0056-0168-70	NDC 0056-0168-90	NDC 0056-0168-75
5 mg peach	NDC 0056-0172-30	NDC 0056-0172-70	NDC 0056-0172-90	NDC 0056-0172-75
6 mg teal		NDC 0056-0189-70	NDC 0056-0189-90	NDC 0056-0189-75
7-1/2 mg yellow		NDC 0056-0173-70		NDC 0056-0173-75
10 mg white (Dye Free)		NDC 0056-0174-70		NDC 0056-0174-75

COUMADIN oral tablet is available in 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 and 10 mg of warfarin sodium with one face inscribed with the word COUMADIN, single scored and imprinted numerically with the 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 or 10 superimposed, and on the other face inscribed with the word "DuPont."

Protect from light. Store in carton until contents have been used. Store at controlled room temperature (59°-86°F, 15°-30°C). Dispense in a tight, light-resistant container as defined in the USP.

Injection: Available for intravenous use only. Not recommended for intramuscular administration. Reconstitute with 2.7 mL of sterile Water for Injection to yield 2 mg/mL. Net contents 5.4 mg lyophilized powder. Maximum yield 2.5 mL.

5 mg vial (box of 6) NDC 0590-0324-35

Protect from light. Keep vial in box until used. Store at controlled room temperature (59°-86°F, 15°-30°C).

After reconstitution, store at controlled room temperature (59°-86°F, 15°-30°C) and use within 4 hours. Do not refrigerate. Discard any unused solution.

CAUTION: Federal law prohibits dispensing without a prescription.

REFERENCES

1. Poller, L.: Laboratory Control of Anticoagulant Therapy. Seminars in Thrombosis and Hemostasis, Vol. 12, No. 1, pp. 13-19, 1986.
2. Hirsh, J.: Is the Dose of Warfarin Prescribed by American Physicians Unnecessarily High? *Arch Int Med*, Vol.147, pp. 769-771, 1987.
3. Cook, D.J., Guyatt, H.G., Laupacis, A., Sackett, D.L.: Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents. Chest ACCP Consensus Conference on Antithrombotic Therapy. *Chest*, Vol. 102(Suppl), pp. 305S-311S, 1992.
4. Hirsh, J., Dalen, J., Deykin, D., Poller, L.: Oral Anticoagulants Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. Chest ACCP Consensus Conference on Antithrombotic Therapy. *Chest*, Vol. 102(Suppl), pp. 312S-326S, 1992.
5. Hirsh, J., M.D., F.C.C.P.: Hamilton Civic Hospitals Research Center, Hamilton, Ontario. Personal Communication.

DuPont Pharma
Wilmington, Delaware 19880

DU PONT PHARMA

COUMADIN® and the color and configuration of COUMADIN tablets are trademarks of The DuPont Merck Pharmaceutical Company. Any unlicensed use of these trademarks is expressly prohibited under the U.S. Trademark Act.
Printed in U.S.A. Copyright © DuPont Pharma 1998

6193-18/Rev. April, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09218/S086/S090/S091

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

150.1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

MAY 18 1998

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

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

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)
(b)(4)

3. Supplement 090 provides for the following revisions to the PRECAUTIONS section:

a. In the list of ENDOGENOUS FACTORS (b)(4)
(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)
(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

The Agency should re-iterate the request in an approvable letter.

Not initiating the requested changed is UNACCEPTABLE.

Conclusions

APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

/S/ 05/19/98
Karen Oliver, RN, MSN
Regulatory Health Project Manager

cc:
Original 09-218/S-086 & S-090
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico /S/ 5-18-98
HFD-180/K.Sizer
HFD-180/M.Ysern

/S/ 5-18-98

draft: KO/January 5, 1998
final: KO/05/18/98/c:\mydocuments\NDA092188-01-S86&90labrev

CSO REVIEW

DU PONT
MERCK

ORIGINAL

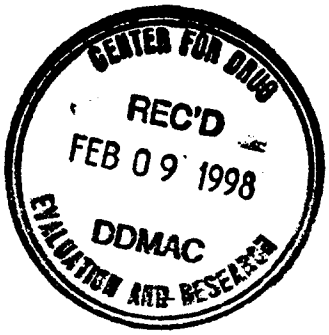
REGULATORY AFFAIRS

DuPont Merck Plaza, Maple Run 2148
Centre Road
Wilmington, DE 19805
Phone: (302) 892-7222
Fax: (302) 992-3011

VIA FACSIMILE

RICHARD S. LEVY, M.D.
Vice President, Worldwide Regulatory Affairs

February 6, 1998



Thomas W. Abrams
Division of Drug Marketing, Advertising
and Communications
HFD-40, Room 17 B-17
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

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

Dear Mr. Abrams:

APPEARS THIS WAY
ON ORIGINAL

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:

APPEARS THIS WAY
ON ORIGINAL

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,

APPEARS THIS WAY
ON ORIGINAL

Richard S. Levy, M.D.
Vice President, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DU PONT
MERCK

REGULATORY AFFAIRS

DuPont Merck Plaza, Maple Run
Centre Road
Wilmington, DE 19805
Fax: (302) 892-0712

May 20, 1998

Desk Copy: Ms. Karen Oliver

Via Federal Express

ORIGINAL

SLR/086

Please

SLR-090

5/21/98 /S/

SLR/091

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 Burka

APPEARS THIS WAY ON ORIGINAL

Maida S. Burka
Director, Regulatory Affairs
Phone: (302) 892-1873
Fax: (302) 892-0712

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 09-218

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

JAN 12 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,

/S/ 1-13-98

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

APPEARS THIS WAY
ON ORIGINAL

Enclosures: (2)

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

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

GENERAL CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

U.S. Food and Drug Administration

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

15 December 1997

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

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

APPEARS THIS WAY
ON ORIGINAL

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

MAR 23 1998

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.

APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

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;1:804), 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®.

3 Page(s) Redacted

DRAFT LABELING

APPEARS THIS WAY
ON ORIGINAL

/S/ 3/21/98
Kurt Sizer, M.D.

cc:
NDA 9-218
HFD-180
HFD-180/LTalarico /S/ 3-23-98
HFD-180/KSizer
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 3/20/98 jgw
MED\N\9218803.0KS

APPEARS THIS WAY
ON ORIGINAL

DU PONT
MERCK

REGULATORY AFFAIRS

DuPont Merck Plaza, Maple Run
Centre Road
Wilmington, DE 19805
Fax: (302) 892-0712

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

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

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 concurrenee.

Sincerely,

Maida Burka
DuPont Merck Pharmaceutical Company
Director Regulatory Affairs
Telephone: (302) 892- 1873
Facsimile: (302) 892-0712

APPEARS THIS WAY
ON ORIGINAL

DU PONT
MERCK

REGULATORY AFFAIRS

DuPont Merck Plaza, Maple Run
Centre Road
Wilmington, DE 19805
Fax: (302) 892-0712

Desk Copy: Ms. Karen Oliver

VIA FEDERAL EXPRESS

ORIGINAL

MAY 08 1998

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:

/S/ 5-12-98

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,

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

Submitted in Duplicate

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

APR 16 1998

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/ 4/16/98

Karen Oliver
Regulatory Health Project Manager

cc:
Original 09-218
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Sizer
HFD-180/M.Ysern
draft: KO/April 1, 1998
final: KO/04/16/98/c:\wpwin\karenfil\rev\09218804.0ko

4-16-98

APPEARS THIS WAY
ON ORIGINAL

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

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

JUN - 1 1998

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.

APPEARS THIS WAY
ON ORIGINAL

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/ 06/01/98

Karen Oliver, RN, MSN
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 6-1-98

APPEARS THIS WAY
ON ORIGINAL

cc:

Original 09-218/S-086, 090, and 091
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Sizer
HFD-180/M.Ysern

APPEARS THIS WAY
ON ORIGINAL

draft: KO/May 15, 1998
final: KO/06/01/98/c:\mydocuments\NDA092186-01-98-S-086-090-091labrev

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL