CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 9-218/S-101

Name: Coumadin® Tablets and Coumadin® Injection

Sponsor: Bristol-Myers Squibb Company

Approval Date: September 2, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 9-218/S-101

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Division Director's Memo	
Labeling Reviews	**X**
Medical Review	
Chemistry Review	
Environmental Assessment	
Pharmacology / Toxicology Review	
Statistical Review	
Microbiology Review	
Clinical Pharmacology & Biopharmaceutics Review	
Administrative and Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 9-218/S-101

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 9-218/S-101

Bristol-Myers Squibb Company
Attention: David L. Silberstein
Associate Director
New Opportunities and Product Development
Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated April 6, 2005, received April 7, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for COUMADIN® Tablets (Warfarin Sodium Tablets, USP) Crystalline and COUMADIN® for Injection (Warfarin Sodium for Injection, USP).

This "Changes Being Effected" supplemental new drug application provides for revisions to the Coumadin package insert to include information relating to drug interactions with Proton Pump Inhibitors (PPIs) and language cautioning against the ingestion of cranberry products, which have been reported to affect the response of patients to Coumadin.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text with the correction listed below.

> In the seventh paragraph, first sentence of the **DOSAGE AND ADMINISTRATION s**ection that reads "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." in the final printed labeling (FPL) to this supplement, retain the bolding, as in the currently approved labeling.

The FPL must be identical, and include the revision indicated, to the enclosed labeling (text for the package insert) and/or submitted labeling (package insert submitted April 6, 2005). This revision is a term of the approval of this application.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 9-218/S-101**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathy Robie-Suh
9/2/2005 02:46:13 PM
signing for Dr. Joyce Korvick

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 9-218/S-101

LABELING

Bristol-Myers Squibb Company

Rx only

COUMADIN® TABLETS

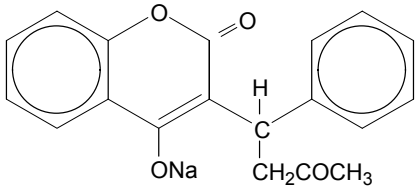
Anticoagulant **(Warfarin Sodium Tablets, USP) Crystalline**

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:



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.

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

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

Asians

Asian patients may require lower initiation and maintenance doses of warfarin. One non-controlled study conducted in 151 Chinese outpatients reported a mean daily warfarin requirement of 3.3±1.4 mg to achieve an INR of 2 to 2.5. These patients were stabilized on warfarin for various indications. Patient age was the most important determinant of warfarin requirement in Chinese patients with a progressively lower warfarin requirement with increasing age.

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 (IV) 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 IV 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*

	N				Thromboembolism		% Major Bleeding	
Study	Warfarin-Treated Patients	Control Patients	PT Ratio	INR	% 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=(I - 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.

INDICATIONS AND USAGE

COUMADIN 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 stillbirth 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 warfarin sodium 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 (Warfarin Sodium), 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: Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that some breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times, although not as prolonged as those of the mothers. The decision to breast-feed should be undertaken only after careful consideration of the available alternatives. Women who are breast-feeding and anticoagulated with warfarin should be very carefully monitored so that recommended PT/INR values are not exceeded. It is prudent to perform coagulation tests and to evaluate vitamin K status in infants at risk for bleeding tendencies before advising women taking warfarin to breast-feed. 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 medications, including botanicals, 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, including botanicals, 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 cancer collagen vascular disease congestive heart failure	diarrhea elevated temperature hepatic disorders infectious hepatitis jaundice	hyperthyroidism poor nutritional state 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	Antiplatelet Drugs/Effects	Leukotriene Receptor Antagonist
Adrenergic Stimulants, Central	Antithyroid Drugs†	Monoamine Oxidase Inhibitors
Alcohol Abuse Reduction Preparations	Beta-Adrenergic Blockers	Narcotics, prolonged
Analgesics	Cholelitholytic Agents	Nonsteroidal Anti-Inflammatory Agents
Anesthetics, Inhalation	Diabetes Agents, Oral	Proton Pump Inhibitors
Antiandrogen	Diuretics†	Psychostimulants
Antiarrhythmics†	Fungal Medications, Intravaginal, Systemic†	Pyrazolones
Antibiotics†	Gastric Acidity and Peptic Ulcer Agents†	Salicylates
Aminoglycosides (oral)	Gastrointestinal Prokinetic Agents	Selective Serotonin Reuptake Inhibitors
Cephalosporins, parenteral	Ulcerative Colitis Agents	Steroids, Adrenocortical†
Macrolides	Gout Treatment Agents	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Miscellaneous	Hemorrheologic Agents	Thrombolytics
Penicillins, intravenous, high dose	Hepatotoxic Drugs	Thyroid Drugs
Quinolones (fluoroquinolones)	Hyperglycemic Agents	Tuberculosis Agents†
Sulfonamides, long acting	Hypertensive Emergency Agents	Uricosuric Agents
Tetracyclines	Hypnotics†	Vaccines
Anticoagulants	Hypolipidemics†	Vitamins†
Anticonvulsants†	Bile Acid-Binding Resins†	
Antidepressants†	Fibric Acid Derivatives	
Antimalarial Agents	HMG-CoA Reductase Inhibitors†	
Antineoplastics†		
Antiparasitic/Antimicrobials		

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

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 hereditary coumarin resistance hyperlipemia	hypothyroidism nephrotic syndrome

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 Antacids Antianxiety Agents Antiarrhythmics† Antibiotics† Anticonvulsants† Antidepressants† Antihistamines Antineoplastics†	Antipsychotic Medications Antithyroid Drugs† Barbiturates Diuretics† Enteral Nutritional Supplements Fungal Medications, Systemic† Gastric Acidity and Peptic Ulcer Agents† Hypnotics†	Hypolipidemics† Bile Acid-Binding Resins† HMG-CoA Reductase Inhibitors† Immunosuppressives Oral Contraceptives, Estrogen Containing Selective Estrogen Receptor Modulators Steroids, Adrenocortical† Tuberculosis Agents† Vitamins†

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

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.

Botanical (Herbal) Medicines

Caution should be exercised when botanical medicines (botanicals) are taken concomitantly with COUMADIN. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.

Specific botanicals reported to affect COUMADIN therapy include the following:

- Bromelains, danshen, dong quai *(Angelica sinensis)*, garlic, Ginkgo biloba, ~~and~~ ginseng, and cranberry products are associated most often with an INCREASE in the effects of COUMADIN.
- Coenzyme Q_{10} (ubidecarenone) and St. John's wort are associated most often with a DECREASE in the effects of COUMADIN.

Some botanicals may cause bleeding events when taken alone (e.g., garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN. Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of COUMADIN.

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed.

Botanicals that contain coumarins with potential anticoagulant effects:		
Alfalfa	Celery	Parsley
Angelica (Dong Quai)	Chamomile	Passion Flower
Aniseed	(German and Roman)	Prickly Ash (Northern)
Arnica	Dandelion[3]	Quassia
Asa Foetida	Fenugreek	Red Clover
Bogbean[1]	Horse Chestnut	Sweet Clover
Boldo	Horseradish	Sweet Woodruff
Buchu	Licorice[3]	Tonka Beans
Capsicum[2]	Meadowsweet[1]	Wild Carrot
Cassia[3]	Nettle	Wild Lettuce

Miscellaneous botanicals with anticoagulant properties:		
Bladder Wrack *(Fucus)*	Pau d'arco	

Botanicals that contain salicylate and/or have antiplatelet properties:		
Agrimony[4]	Dandelion[3]	Meadowsweet[1]
Aloe Gel	Feverfew	Onion[5]
Aspen	Garlic[5]	Policosanol
Black Cohosh	German Sarsaparilla	Poplar
Black Haw	Ginger	Senega
Bogbean[1]	Ginkgo Biloba	Tamarind
Cassia[3]	Ginseng *(Panax)*[5]	Willow
Clove	Licorice[3]	Wintergreen

Botanicals with fibrinolytic properties:		
Bromelains	Garlic[5]	Inositol Nicotinate
Capsicum[2]	Ginseng *(Panax)*[5]	Onion[5]

Botanicals with coagulant properties:		
Agrimony[4]	Mistletoe	
Goldenseal	Yarrow	

[1]Contains coumarins and salicylate.
[2]Contains coumarins and has fibrinolytic properties.
[3]Contains coumarins and has antiplatelet properties.
[4]Contains salicylate and has coagulant properties.
[5]Has antiplatelet and fibrinolytic properties.

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), other over-the-counter medications, and botanical (herbal) products (e.g., bromelains, coenzyme Q_{10}, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John's wort) 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. You should also avoid intake of cranberry juice or any other cranberry products. Notify your health care provider if any of these products are part of your normal diet. 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.

Geriatric Use

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see **CLINICAL PHARMACOLOGY**). COUMADIN is contraindicated in any unsupervised patient with senility. Caution should be observed with administration of warfarin sodium to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Lower initiation and maintenance

doses of COUMADIN are recommended for elderly patients (see **DOSAGE AND ADMINISTRATION**).

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**~~ **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, pruritus, 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.

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. Lower initiation and maintenance 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**). Based on limited data, Asian patients may also require lower initiation and maintenance doses of COUMADIN (see **CLINICAL PHARMACOLOGY**). 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 IV 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, was 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 with one face imprinted numerically with 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 or 10 superimposed and inscribed with "COUMADIN" and with the opposite face plain. COUMADIN is available in bottles and Hospital Unit-Dose Blister Packages with potencies and colors as follows:

	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 0056-0170-70	NDC 0056-0170-90	NDC 0056-0170-75
2-1/2 mg green	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 0056-0172-70	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~~

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

Hospital Unit-Dose Blister Packages are to be stored in carton until contents have been used.

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.

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.

Distributed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Printed in U.S.A.
1170696A1 ~~6572-01/Rev. June, 2002~~Revised April 2005
1187090

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 9-218/S-101

LABELING REVIEWS

Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

PROJECT MANAGEMENT LABELING REVIEW

Application Number: NDA 9-218/S-101

Name of Drug: Coumadin® (warfarin sodium tablets, USP) 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg and Coumadin® (warfarin sodium for injection, USP), 5 mg vial

Sponsor: Bristol Myers Squibb Company.

Materials Reviewed: Package Insert (PI)
Medication Guide

Submission Date: April 6, 2005

Receipt Date: April 7, 2005

Background and Summary

Background:

Coumadin® was approved on June 8, 1954 for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism; prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. The most recently approved labeling is in SLR-099 dated June 2, 2002.

In a ODS Postmarketing Safety Review dated January 8, 2002, for Prevacid, Aciphex, Protonix, Nexium and Coumadin, Ann Corken Mackey, R. Ph., M.P.H., made the following recommendations: "Since healthcare providers consult the labeling for guidance involving drug interactions with warfarin and the interaction is labeled for omeprazole, the pantoprazole and esomeprazole labeling should be updated to reflect the postmarketing reports of increases in INR with clinical outcomes. The evidence for lansoprazole and rabeprazole is not as compelling, so consideration should be given to including in the labeling for these drugs that postmarketing reports of INR increases with clinical outcomes have been received for other proton pump inhibitors. In addition, lansoprazole, rabeprazole, pantoprazole, and esomeprazole should all be added to the warfarin labeling as causing increased INR/PT, possibly as class labeling.

The Agency sent Bristol-Myers Squibb Company a letter dated August 9, 2004, requesting that they submit a Changes Being Effected "CBE" supplement to the Coumadin NDA to revise the labeling information as follows:

"We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

> Under the **PRECAUTIONS** section, add "Proton Pump Inhibitors" to the "Classes of Drugs" section of the table of exogenous factors that may be responsible for INCREASED PT/INR response due to potential drug interactions with Coumadin®. In addition, the following drugs should be added (in proper alphabetical position) to the Specific Drugs Reported portion of the same table: esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole."

In a ODS Postmarketing Safety Review for Warfarin dated February 8, 2005, Ann Corken Mackey, R.Ph., MPH, Safety Evaluator, reported a concern regarding a possible interaction between warfarin and cranberry juice (Vaccinium macrocarpon). The United Kingdom (UK) announced in October 2004 that they were revising the label for warfarin to include an interaction between warfarin and cranberry juice, based on cases reported to their agency. Cranberry juice contains antioxidants including flavonoids which are known to inhibit cytochrome P 450 activity and warfarin is metabolized by CYP2C9, so it is possible that cranberry juice could interfere with its metabolism. The warfarin labeling contains a section of botanical (herbal) products that may interact with warfarin and recommends that patient's INR/PT be monitored when initiating or discontinuing these products. Based on the case reports described in the review document and actions undertaken by the UK, the ODS reviewer recommended that a potential for increased INR or PT in patients taking warfarin and using cranberry products, should be added to the warfarin label.

The sponsor submitted the CBE labeling supplement SLR-101 on April 6, 2005 (received April 7, 2005) containing final printed labeling for the package insert. The sponsor also included language cautioning against the ingestion of cranberry products, which have been reported to affect the response of patients to Coumadin.

Review

I. Package Insert

The PI for Coumadin (warfarin sodium tablets, USP) in SLR-101 (submitted April 6, 2005; received April 7, 2005) identified as "1170696A1 1187090 Revised April 2005" was compared to the PI for Coumadin (warfarin sodium tablets, USP) in SLR-099 (submitted November 27, 2001; received November 28, 2001; approved May 3, 2002) identified as Insert Code "6572-01/Rev. June, 2002. The PI's are identical except for the following:

A. **PRECAUTIONS** section

1. "EXOGENOUS FACTORS" table

a. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Classes of Drugs**," in the third column, following the term "nonsteroidal Anti-Inflammatory Agents" the sponsor added the term "Proton Pump Inhibitors."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of Proton Pump Inhibitors to this section of the table. The addition is acceptable.

b. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the first column, following the name "erythromycin" the sponsor added the name "esomeprazole."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

c. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the second column, following the name "fluvoxamine" the sponsor added the name "gefitinib."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

d. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the second column, following the name "ketorolac" the sponsor added the name "lansoprazole."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

e. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the second column, following the name "omeprazole" the sponsor added the name "oxandrolone."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone,

pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

f. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the third column, the sponsor inserted the name "pantoprazole" before the first name "paroxetine."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

g. In the table entitled "EXOGENOUS FACTORS," under the section entitled "**Specific Drugs Reported**," in the third column, following the name "quinine" the sponsor added the name "rabeprazole."

The addition is in response to the Agency August 9, 2004, letter requesting the addition of "esomeprazole, gefitinib, Iansoprazole, oxandrolone, pantoprazole, and rabeprazole" to this section of the table. The addition is acceptable.

2. In the **Botanical (Herbal) Medicines** subsection, in the second paragraph, first bullet that begins "Bromelains, danshen, dong quai . . ." the sponsor deleted the term "and" following "Ginkgo biloba" and added the phrase "and cranberry products" following the term "ginseng" so that the bullet reads "Bromelains, danshen, dong quai (Angelica sinensis), garlic, Ginkgo biloba, ginseng, and cranberry products are associated most often with an INCREASE in the effects of COUMADIN."

The addition of cranberry products to the list of botanical medicines that interact with Coumadin is acceptable. (See ODS review by Ann Corken Mackey, R.Ph., M.P.H. dated February 8, 2005. The revision is acceptable.

3. In the **Information for Patients** subsection, in the first paragraph, following the thirteenth sentence that begins "Avoid drastic changes in dietary habits . . . " the sponsor added the following two sentences:

"You should also avoid intake of cranberry juice or any other cranberry products. Notify your health care provider if any of these products are part of your normal diet."

The addition of the two sentences is acceptable. (See ODS review by Ann Corken Mackey, R.Ph., M.P.H. dated February 8, 2005.

B. **ADVERSE REACTIONS** section

In the first paragraph, first bullet, in the seventh sentence that reads "(See OVERDOSAGE-Treatment)." the sponsor replaced the dash with added a colon after the term "OVERDOSAGE" and bolded the term "OVERDOSAGE" so that the sentence reads "(See **OVERDOSAGE**: Treatment.)

The revision is editorial and acceptable.

C. **DOSAGE AND ADMINISTRATION** section

The sponsor unbolded the seventh paragraph, first sentence that reads "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."

The paragraph should be bolded. The sponsor confirmed in a telephone conversation between Diane Moore, FDA Regulatory Project Manager, and David l. Silberstein, Associate Director, New Opportunities and Product Development, Global Regulatory Strategy, Bristol-Myers Squibb Company on September 1, 2005, that the sponsor inadvertently unbolded the above sentence in the DOSAGE AND ADMINISTRATION section. The sentence should be bolded in the FPL.

D. **HOW SUPPLIED** section

1. Following the first paragraph that begins "**Tablets** For oral use, . . ." the sponsor deleted the NDC numbers for the fifth, eighth and ninth tablet presentations: 4 mg blue "NDC 0056-0168-75", 7-1/2 mg yellow "NDC 0056-0173-75" and 10 mg white (Dye Free) "NDC 0056-0174-75", respectfully.

   The revisions are editorial and acceptable.

2. Following the references, the sponsor revised the third paragraph of the manufacturer information that reads "Copyright © Bristol-Myers Squibb Company 2002" to read "Copyright © Bristol-Myers Squibb Company 2005"

   The revision is editorial and acceptable.

3. Following the copyright sentence, the sponsor revised the revised date and identification number from "6572-01/Rev. June, 2002" to "1170696 A11187090 Revised April 2005"

   The revisions are editorial and acceptable.

Conclusions

1. The labeling should be approved with the requirement that the sponsor rebold the seventh paragraph, first sentence of the **DOSAGE AND ADMINISTRATION s**ection that reads "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" in the FPL to this supplement.

_____
Diane Moore, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Drafted: dm/August 31, 2005
Finalized: September 1, 2005
Filename: N9218S101LblRev.doc

RPM LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
9/2/2005 10:49:54 AM
CSO

Brian Strongin
9/2/2005 11:36:30 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 9-218/S-101

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

David L. Silberstein
Associate Director
New Opportunities & Product Development
Pharmaceutical Research Institute

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-4317 Fax 609-252-6153
david.silberstein@bms.com

Bristol-Myers Squibb Company

**SPECIAL SUPPLEMENT - FINAL PRINTED LABELING:
CHANGES BEING EFFECTED**

NDA 09-218
COUMADIN®Tablets (Warfarin Sodium Tablets, USP) Crystalline and COUMADIN® for Injection (Warfarin Sodium for Injection, USP)

April 6, 2005

Joyce Korvick, M.D., M.P.H., Acting Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office for Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Korvick:

Reference is made to the Agency's letter dated August 9, 2004, requesting that we submit a Changes Being Effected supplement to this NDA, revising labeling information for Coumadin®.

This submission provides a final printed Coumadin® package insert and related documentation outlining the specific changes, in accordance with the FDA Guidance on Providing Regulatory Submissions in Electronic Format. In addition to the requested information relating to drug interactions with Proton Pump Inhibitors (PPIs), we have also included language cautioning against the ingestion of cranberry products, which have been reported to affect the response of patients to Coumadin.

If I can provide any further information or assistance on this submission, please feel free to contact me by phone (609-252-4317) or FAX (609-252-6153).

Sincerely,

David L. Silberstein
Associate Director,
New Opportunities and Product Development
Global Regulatory Strategy

DLS/kr
Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 9-218/SLR-101 **CBE-30/CBE-0 SUPPLEMENT**

Bristol-Myers Squibb Company
Attention: David L. Silberstein
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Coumadin® (warfarin sodium tablets, USP) 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, and 10 mg, and Coumadin® (warfarin sodium for injection, USP), 5 mg vial.
NDA Number:	9-218
Supplement number:	101
Date of supplement:	April 6, 2005
Date of receipt:	April 11, 2005

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following changes: changes to the package insert to add interaction with proton pump inhibitors and interaction with cranberry juice.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 10, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 11, 2005.

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road

Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-9334.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alice Kacuba

4/27/05 03:56:13 PM