CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09-218/S097

APPROVAL LETTER

NDA 09-218/S-097

FEB 17 2000

DuPont Pharmaceuticals Company
Attention: James L. Gaskill, R.Ph.
Chestnut Run Plaza, MR2146
974 Centre Road
Wilmington, DE 19805

Dear Mr. Gaskill:

Please refer to your supplemental new drug application dated November 12, 1999, received November 17, 1999, 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.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the following: in the PRECAUTIONS section, the "EXOGENOUS FACTORS" subsection (factors that may be responsible for INCREASED PT/INR response), the "Specific Drugs Reported" table, the addition of the drug names "celecoxib", "rofecoxib", and "capecitabine". Your submission stated January 4, 2000 as the implementation date for the changes.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling submitted November 12, 1999. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

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, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

/S/ 2-17-00

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09-218/S097

APPROVABLE LETTER

NDA 9-218/S-097

DuPont Pharmaceuticals Company
Attention: James L. Gaskill, R.Ph.
Chestnut Run Plaza, MR2146
974 Centre Road
Wilmington, Delaware 19805

NOV 29

Dear Mr. Gaskill:

We have received your supplemental 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) Tablets
Coumadin® (Warfarin Sodium for Injection) for Injection
NDA Number: 9-218

Supplement Number: S-097

Date of Supplement: November 12, 1999

Date of Receipt: November 17, 1999

This supplemental application, submitted as "Supplement – Changes Being Effected" proposes the following change: in the PRECAUTIONS section, the "EXOGENOUSE FACTORS" (factors that may be responsible for INCREASED PT/INR response), the "Specific Drugs Reported" table, the following drug names have been added: celecoxib, rofecoxib, and capecitabine. In your submission you state that the change to the package insert will be implemented January 4, 2000.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 16, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

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

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact me at (301) 827-7310.

Sincerely,

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

cc:
Archival NDA 9-218/S-097
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: mk 11/23/99
Initialed by: K. Oliver 11/29/99
final: M. Kidwell 11/29/99 11/29/99
filename:

-BE-0 / SUPPLEMENT ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09-218/S097

FINAL PRINTED LABELING

6466-03/Rev. October, 1999

COUMADIN® TABLETS

Anticoagulant (Warfarin Sodium Tablets, USP) Crystalline

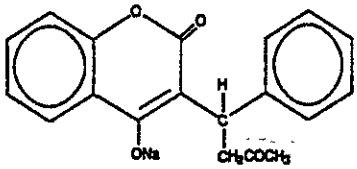
R_x only

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.

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

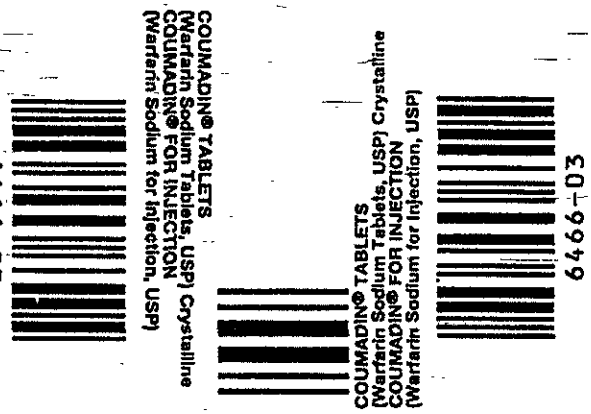
Event	Warfarin (N=607)	Placebo (N=607)	RR (95%CI)	% Risk Reduction (p-value)
Total Patient Years of Follow-up	2018	1944		
Total Mortality	94 (4.7/100 py)	123 (6.3/100 py)	0.76 (0.60, 0.97)	24 (p=0.030)
Vascular Death	82 (4.1/100 py)	105 (5.4/100 py)	0.78 (0.60, 1.02)	22 (p=0.068)
Recurrent MI	82 (4.1/100 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.



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 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, 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.)

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 infectious hepatitis jaundice
cancer	hyperthyroidism
collagen vascular disease	poor nutritional state
congestive heart failure	steatorrhea
diarrhea	vitamin K deficiency
elevated temperature	

EXOGENOUS FACTORS:

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

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

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

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†
atorvastatin	ethchlorvynol	primidone
azathioprine	glutethimide	propylthiouracil†
butabarbital	griseofulvin	ranitidine†
butalbital	haloperidol	rifampin
carbamazepine	meprobamate	secobarbital
chloral hydrate†	6-mercaptopurine	spironolactone
chlordiazepoxide	methimazole†	sucralfate
chlorthalidone	moricizine hydrochloride†	trazodone
cholestyramine†	nafcillin	vitamin C (high dose)
corticotropin	paraldehyde	vitamin K
cortisone	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.

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. Low initiation doses of warfarin 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.)
- 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. 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 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 2.0	ISI 1.8	ISI 1.6	ISI 1.4	ISI 1.2
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 inscribed with "DuPont." 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 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.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09-218/S097

ADMINISTRATIVE DOCUMENTS

U.S. Food and Drug Administration

This is the retyped text of a letter from Roche Laboratories, Inc. Contact the company for a copy of any referenced enclosures.

March 1999

Important Prescribing Information: Potential Xeloda Interaction with Coumarin Derivatives

Dear Doctor:

The Drug Safety Department of Hoffman-La Roche has received reports of altered coagulation parameters and/or bleeding in cancer patients on Xeloda (capecitabine) who were taking coumarin derivatives concomitantly. The time of occurrence of these events (altered coagulation parameters and/or bleeding) ranged from several days to several months after starting Xeloda therapy and in isolated cases, occurred within one month after the last dose of Xeloda. The mechanism of action whereby Xeloda might alter coagulation parameters is unclear and will be further investigated. Apart from the known difficulties of sustaining stable INR's in cancer patients, there may have been confounding variable underlying the alterations in coagulation such as trauma, dietary changes or inconsistencies, hepatic dysfunction, hypermetabolic states, and concomitant use of other agents that have the potential to interact with coumarin derivatives.

After discussion and review of these reports with the FDA, we feel at this time that an effect of Xeloda on coagulation parameters in patients taking concomitant warfarin or related coumarin derivative anticoagulants cannot be ruled out. However, because of the potential clinical significance of such an interaction, Hoffman-La Roche recommends that patients taking Xeloda with concomitant coumarin derivatives should be monitored regularly for alterations in their coagulation parameters (PT or INR). If your patient's anticoagulant therapy is being prescribed and/or monitored by another physician, please inform them of the above information.

Please note that the following new information has been added to two sections of the package insert. These include:

WARNINGS:

General:

Coagulopathy: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. The events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in-patients with and without liver metastases. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

PRECAUTIONS:

***Drug-Drug Interactions*:** Interaction with coumarin anticoagulants: Altered coagulation parameters

and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

The medical community can further our understanding of these events by reporting all cases to Hoffman-La Roche at 1-800-526-6367 or the FDA MedWatch program by phone at 1-800-FDA-1088, by Fax 1-800-FDA-1078 or by mail: MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

The new package insert is enclosed for your information. If you have any questions, please call Roche Professional Product Information at 1-800-526-6367.

Sincerely,

Fabio Benedetti, M.D.
Medical Director

Roche Laboratories, Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Return to Summary

FEB 17 2000

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 09-218/S-097

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

Sponsor: DuPont Pharmaceuticals Company

Material Reviewed

Submission Date(s): November 12, 1999

Receipt Date(s): November 17, 1999

Background and Summary Description: Supplement 097, submitted as "Special Supplement-Changes Being Effected", provides for the following change: in the PRECAUTIONS section, the "EXOGENOUS FACTORS" subsection (factors that may be responsible for INCREASED PT/INR response), the "Specific Drugs Reported" table, the addition of the drug names "celecoxib", "rofecoxib", and "capecitabine".

Review

The FPL package insert, identified as "6466-01/Rev.October, 1999", was compared to the package insert, identified as "6466-02/Rev. October, 1999", approved July 9, 1999 in supplement 096. (NOTE: The firm informed the Agency that the Coumadin package insert configuration "6193" will be discontinued upon the implementation of this supplement.) The implementation date for this supplement is January 4, 2000. The package inserts are identical except for the following:

1. The identification codes were changed.

   This change is ACCEPTABLE.

2. At the bottom of the first column of the package insert, the numbers below the bar codes have been changed:

   from: "6466-02"
   to: "6466-03".

   This change is ACCEPTABLE.

3. In the PRECAUTIONS section, in the EXOGENOUS FACTORS subsection (factors that may be responsible for INCREASED PT/INR response), the "Specific Drugs Reported" table, the drug names "celecoxib", "rofecoxib", and "capecitabine" have been added.

These additions, requested in an October 13, 1999 Agency letter, are ACCEPTABLE.

Conclusions

1. The identified changes are ACCEPTABLE.

2. An approval letter should be issued.

/S/ 2/17/00
Karen Oliver, RN, MSN
Regulatory Health Project Manager

/S/ 2-17-00

cc:
Original NDA 09-218/S-097
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/L.Zhou
HFD-180/M.Ysern
draft: KO/February 17, 2000
final: KO/02/17/00/

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
9-218

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DuPont Pharmaceuticals Company	November 12, 1999
TELEPHONE NO. *(Include Area Code)* (302) 892-7308	**FACSIMILE (FAX) Number** *(Include Area Code)* (302) 892-0712

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

Chestnut Run Plaza, Maple Run
974 Centre Road
Wilmington, DE 19805

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 9-218

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Warfarin Sodium, USP	Coumadin

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets, Injection	1,2,2.5,3,4,5,6,7.5 & 10mg; 5mg/vial	Oral, IV

(PROPOSED) INDICATION(S) FOR USE: Prophylaxis and/or treatment of venous thrombosis and extensions, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement. To reduce the risk of death, recurrent MI and thromboembolic events ie, stroke or systemic embolization after MI

APPLICATION INFORMATION

APPLICATION TYPE (check one) ■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug ___ Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ■ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Final Printed Labeling - Special Supplement - CBE

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

SEE ATTACHED

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND No. ___
DMF ___

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☐ Draft Labeling ■ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports ~~forms~~ (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	James L. Gaskill, R.Ph. Associate Director, Regulatory Affairs	11/12/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Chestnut Run Plaza, MR2146, 974 Centre Road, Wilmington, DE 19805	(302) 892-7308

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Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (7/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 09-218/S097

CORRESPONDENCE

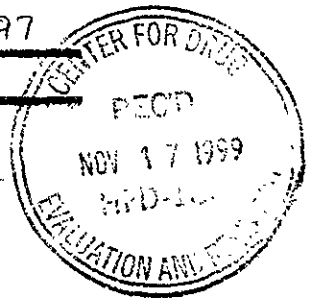
Life Sciences Enterprise
DuPont Pharmaceuticals Company

CERTIFIED MAIL

Desk Copy: K. Oliver (HFD-180)

ORIGINAL

NDA NO. 9-218 REF. NO. 097
NDA SUPPL FOR SCR



November 12, 1999

Lilia Talarico, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 9-218;
Coumadin Tablets (Warfarin Sodium Tablets, USP) Crystalline
Coumadin for Injection (Warfarin Sodium for Injection, USP)
SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

Dear Dr. Talarico,

Reference is made to our NDA for Coumadin® submitted December 15, 1953. Reference is also made to the October 13, 1999 letter from the Division which made the following request:

> In the PRECAUTIONS-section, the "EXOGENOUS FACTORS" (factors that may be responsible for INCREASED PT/INR response), the "Specific Drugs Reported" table, add the following drug names: "Celebrex" and "Vioxx".

As requested, we are submitting final printed labeling including this change as a Special Supplement – Changes Being Effected. The changes have been made as requested in your October 13, 1999 letter (Attachment 1) except that the generic names for Celebrex® and Vioxx® (celecoxib and rofecoxib, respectively) have been used to maintain the consistent use of generic names in this table. This use of the generic names was agreed upon in the October 25, 1999 telephone conversation between K. Oliver of the Division and J. Gaskill of DuPont Pharmaceuticals. In addition to celecoxib and rofecoxib, one additional drug is also being added to the table of specific drugs responsible for increased PT/INR response. Capecitabine (Xeloda®) was the subject of a Dear Doctor letter warning of a potential interaction with coumarin-derivative anticoagulants such as warfarin, and the labeling of capecitabine has been modified to include statements to this effect (see Attachment 2). In addition, two spontaneous reports of elevated PT/INR values in patients taking Coumadin and capecitabine have been reported. Copies of these spontaneous reports are provided in Attachment 3. The table of "Classes of Drugs" that may be responsible for increased PT/INR response is not being modified

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at this time, since both Non-Steroidal Anti-Inflammatory Agents and Antineoplastics are currently listed as classes of drugs which may increased PT/INR response.

These changes are being made to the current Coumadin insert (6466-02/Rev. May 99) which was approved on July 11, 1999 (S-096) and implemented on September 1, 1999. A marked-up copy of the revised PI showing the specific changes is provided in Attachment 4. Twenty copies of the final printed labeling (ten of which are mounted on heavy weight paper) are provided in Attachment 5.

Please note that Coumadin package insert configuration 6193 will be discontinued upon implementation of this supplement. Packaging equipment changes have eliminated the need for multiple configurations of the Coumadin package insert. Upon implementation of this supplement, package insert 6466-03 will be the only insert used with Coumadin tablets and injection.

According to 21 CFR 314.70(c) and the Division's letter of October 13, 1999, the labeling changes in this supplement may be implemented prior to FDA approval. These changes to the package insert will be implemented on January 4, 2000.

Should you have any questions or require any additional information, please contact me at (302) 892-7308.

Sincerely,

James L. Gaskill, R.Ph.
Associate Director, Regulatory Affairs
(302) 892-7308

Enclosures
Submitted in Triplicate

APPEARS THIS WAY
ON ORIGINAL