PRODUCT MONOGRAPH

[Pr]WARFARIN

Warfarin Sodium Tablets, USP

1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg Warfarin Sodium (crystalline clathrate)

ANTICOAGULANT

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[Pr]WARFARIN

Warfarin Sodium, USP (crystalline clathrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg Tablets	Corn Starch, Lactose Monohydrate, Stearic Acid, Magnesium Stearate and colour dye which varies in each tablet strength. 1 mg: FD&C Red #40 Aluminum Lake 2 mg : FD&C Red #40 Aluminum Lake FD&C Blue #2 Aluminum Lake 2.5 mg: FD&C Blue #1 Aluminum Lake HT D&C Yellow #10 Aluminum Lake 3 mg: Lake Blend Brown LB-1685 4 mg : FD&C Blue #1 Aluminum Lake 5 mg : FD&C Yellow #6 Aluminum Lake 6 mg: Lake Blend Dark Green LB-1236 7.5 mg: FD&C Yellow #6 Aluminum Lake D&C Yellow #10 Aluminum Lake 10 mg: Dye free

INDICATIONS AND CLINICAL USE

WARFARIN (warfarin sodium) is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, atrial fibrillation with embolization, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, including stroke, reinfarction.

The following are some of the more common clinical disorders which may be associated with or predispose patients to the above indications:

1. Thrombophlebitis
2. Congestive heart failure
3. Surgical procedure or trauma associated with a high risk of thromboembolism
4. Myocardial infarction
5. Cerebral embolism

It may also be useful as an adjunct in the treatment of transient cerebral ischemic attacks due to intravascular clotting.

CONTRAINDICATIONS

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

- **Pregnancy:**
  WARFARIN (warfarin sodium) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal haemorrhage to the fetus *in utero.* Women of childbearing potential must take precautions not to become pregnant while on WARFARIN therapy. 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 the light of those risks.

- **Haemorrhagic 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 haemorrhage
    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 sodium or to any other components of WARFARIN.

WARNINGS AND PRECAUTIONS

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see PRECAUTIONS), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding. **(See PRECAUTIONS: Information for Patients)**

General:

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. WARFARIN (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 times (PT) ratio/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 WARFARIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

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

Administration of anticoagulants in the following conditions will be based upon clinical judgement in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

1. Severe to moderate hepatic or renal insufficiency.
2. Infectious diseases or disturbances of intestinal flora, such as sprue or as seen with antibiotic use.
3. Trauma which may result in internal bleeding.
4. Surgery or trauma resulting in large exposed raw surfaces.
5. Indwelling catheters**.**
6. Severe to moderate hypertension.
7. 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 warfarin 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.
8. Diseases affecting the microvasculature or microcirculation, such as polycythemia vera, vasculitis, and severe diabetes.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state or medication, or the use of natural medicines, may influence the patient's response to anticoagulants. It is generally good practice to monitor the patienţs response with additional PT ratio/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including natural medicines, are initiated, discontinued or taken irregularly. Tables 1 and 2 provide a listing of factors, alone or in combination, which may effect the PT. However, other factors may also affect the anticoagulant response and the tables are provided for your reference only.

Periodic determination of PT ratio/INR or other suitable coagulation test is essential (See DOSAGE AND ADMINISTRATION : Laboratory Control).

Because a patient may be exposed to a combination of listed factors, the net effect of Warfarin on PT ratio/INR responses may be unpredictable. More frequent PT/INR monitoring is therefore advisable.

Intramuscular 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.

Hematologic:

Hemorrhage
The most serious risks associated with anticoagulant therapy with WARFARIN (warfarin sodium) are haemorrhage in any tissue or organ (see WARNING BOX) and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of haemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Haemorrhage 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.

Anticoagulation therapy with WARFARIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toe syndrome". Discontinuation of WARFARIN therapy is recommended when such phenomena are observed. While the "purple toe syndrome" is reported to be reversible, other complications of microembolization may not be reversible.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toe 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 toe syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled colour of the toe, 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.

A severe elevation (> 50 seconds) in activated partial thromboplastin time (aPTT) with a PT ration/INR in the desired range has been identified as an indication of increased risk of postoperative haemorrhage. This has been noted in patients undergoing elective hip surgery receiving warfarin alone.

Heparin-Induced Thrombocytopenia
WARFARIN (warfarin sodium) should be used with caution in patients with heparin-induced thrombocytopenia and deep vein thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients when heparin treatment was discontinued and warfarin therapy was started or continued especially when large initiation doses were used. In some patients sequelae have included amputation of the involved area and/or death. The use of alternative anticoagulant therapy should be considered in patients with heparin-induced thrombocytopenia and deep vein thrombosis.

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

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

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

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

Patients with congestive heart failure may become more responsive to warfarin, thereby requiring more frequent laboratory monitoring, and reduced doses of WARFARIN.

Special Populations:

Use in Pregnancy: See CONTRAINDICATIONS, Pregnancy.

Use in Nursing Mothers:
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 breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times. 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 INR values are not exceeded. It is prudent to perform coagulation tests on infants at risk for bleeding before advising women taking warfarin to breast-feed. Effects in premature infants have not been evaluated.

Use in Children:
Safety and effectiveness in children below 18 years of age have not been established in randomized, controlled clinical trials. However, the use of WARFARIN in pediatric patients has been documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT ratio/INR ranges in the pediatric patient has been

reported. More frequent PT ratio/INR determinations are recommended because of possible changing warfarin requirements.

Use in Elderly and/or Debilitated Patients: Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see ACTION and CLINICAL PHARMACOLOGY, in the Elderly) is contraindicated in any unsupervised patient with senility. Caution should be exercised with administration of warfarin sodium to elderly and/or debilitated patients in any situation or physical condition where added risk of hemorrhage is present. Low initiation and maintenance doses of WARFARIN (warfarin sodium) are recommended in the elderly (see DOSAGE and ADMINISTRATION).

Considerations for Increased Bleeding Risk

WARFARIN is a narrow therapeutic range (index) drug, and additional caution should be observed when warfarin sodium is administered to certain patients. Reported risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see PRECAUTIONS) and long duration of warfarin therapy. Identification of risk factors for bleeding and certain genetic variations in CYP2CP and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses (see CLINICAL PHARMACOLOGY: Metabolism and DOSAGE AND ADMINISTRATION). Bleeding is more likely to occur during the starting period and with a higher dose of WARFARIN (resulting in a higher INR).

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

Monitoring and Laboratory Tests:

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

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT ratio/INR in the desired range has been identified as an indication of increased risk of postoperative haemorrhage. This has been noted in patients undergoing elective hip surgery receiving warfarin alone.

Because a patient may be exposed to a combination of listed factors, the net effect of WARFARIN on PT ratio/INR responses may be unpredictable. More frequent PT/INR monitoring is therefore advisable.

ADVERSE REACTIONS

Potential adverse reactions to warfarin sodium may include:

- Fatal or nonfatal haemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, and symptoms, and severity will vary according to the location and degree or extent of the bleeding. Haemorrhagic 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 haemorrhage 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 ratio/INR. (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

- Bleeding which occurs when the PT ratio/INR is within the therapeutic range warrants diagnostic investigation, since it may unmask a previously unsuspected lesion, e.g. tumour, ulcer, etc.

- Necrosis of skin and other tissues. (see WARNINGS).

- Adverse reactions reported infrequently include:

  Body As A Whole: hypersensitivity/allergic reactions, pain, edema, asthenia, fever, headache, fatigue, lethargy, malaise, anemia, pallor.
  Central and Peripheral Nervous System: dizziness, cold intolerance, coma, loss of consciousness, syncope and paresthesia, including feeling cold and chills
  Gastrointestinal: nausea, diarrhea, abdominal pain, including cramping, flatulence/bloating, vomiting
  Liver and Biliary: elevated liver enzymes, hepatitis, jaundice, cholestatic hepatic injury
  Skin and Appendages: alopecia, rash, pruritus, urticaria, dermatitis, including bullous eruptions
  Vascular, Extracardiac: angina syndrome, chest pain, systemic cholesterol microembolization, purple toe syndrome, vasculitis
  Special Senses: taste perversion

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.

DRUG INTERACTIONS

Overview

Drugs may interact with WARFARIN (warfarin sodium) through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin

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 warfarin 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 complete in vivo inhibition of the CYP 2C9 isozyme, may be expected to result in lower maintenance dose requirement of warfarin. Individuals with allelic polymorphisms of CYP 2C9 have been identified and have been shown to have lower maintenance dose requirements of warfarin and increased risk of overanticoagulation. Acquired or inherited warfarin resistance should be suspected if large daily doses of WARFARIN (warfarin sodium) are required to maintain a patient's PT ratio/INR within a normal therapeutic range.

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

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

Close monitoring of patients receiving nonsteroidal anti-inflammatory agents (NSAIDs) is recommended to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect prothrombin time, NSAIDs can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT ratio/INR monitoring is advisable. Coumarins may also affect the action of other drugs. Hypoglycaemic 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.

Table 1

The following factors, alone or in combination, may be responsible for INCREASED PT ratio or INR, or INCREASED risk of bleeding:

ENDOGENOUS FACTORS	
blood dyscrasias	hepatic disorders (infectious
cancer	hepatitis, jaundice)
collagen vascular disease	hyperthyroidism
congestive heart failure	poor nutritional state
diarrhea	steatorrhea
elevated temperature	vitamin K deficiency

EXOGENOUS FACTORS:
Potential drug interactions with WARFARIN are listed below by drug class and by specific drugs.

Classes of Drugs

5-lipoxygenase Inhibitors	Antiparasitic/ Antimicrobials	Lipid Lowering Agents*
Adrenergic Stimulants, Central	Antiplatelet Drugs/Effects	Bile Acid-Binding Resins*
Alcohol Abuse Reduction Preparations	Antithyroid Drugs*	Fibrates
Analgesics	Beta-Adrenergic Blockers	HMG-CoA Reductase Inhibitors*
Anaesthetics, Inhalation	Cholelitholytic Agents	Monoamine Oxidase Inhibitors
Antiandrogens	Diabetes Agents, Oral	Narcotics, prolonged
Antiarrhythmics*	Diuretics*	Natural medicines
Antibiotics*	Gastric Acidity and Peptic Ulcer Agents*	Nonsteroidal Anti-Inflammatory Agents
Aminoglycosides (oral)	Gastrointestinal, Ulcerative Colitis Agents	Cox-2 Inhibitors
Cephalosporins, parenteral	Gastrointestinal, Prokinetic Agents	Nonselective NSAIDS
Macrolides	Gout Treatment Agents	Psychostimulants
Penicillins, intravenous, high dose	Hemorrheologic Agents	Pyrazolones
Quinolones (fluoroquinolones)	Hepatotoxic Drugs	Salicylates
Sulfonamides, long acting	Hyperglycemic Agents	Selective Serotonin Reuptake Inhibitors
Tetracyclines	Hypertensive Emergency Agents	Steroids, Adrenocortical*
Anticoagulants	Hypnotics*	Steroids, Anabolic (17- Alkyl Testosterone Derivatives)
Anticonvulsants*	Leukotriene Receptor Antagonists	Thrombolytics
Antidepressants*		Thyroid Drugs
Antifungal Medications, Intravaginal, Systemic*		Tuberculosis Agents*
Antimalarial Agents		Uricosuric Agents
Antineoplastics*		Vaccines
		Vitamins*

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

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

*** Increased and decreased PT ratio/INR responses have been reported.**

Table 2

The following factors, alone or in combination, may be responsible for DECREASED PT ratio or INR, or increased potential risk of thromboembolic events:

ENDOGENOUS FACTORS:		
edema hereditary coumarin resistance	hyperlipemia hypothyroidism	nephrotic syndrome
EXOGENOUS FACTORS: **Potential drug interactions with WARFARIN are listed below by drug class and by specific drugs.**		
Classes of Drugs		
Adrenal Cortical Steroid Inhibitors Antacids Antianxiety Agents Antiarrhythmics* Antibiotics* Anticonvulsants* Antidepressants* Anti - Fungal Medications, Systemic* Antihistamines Antineoplastics*	Antipsychotic Medications Antithyroid Drugs* Barbiturates Diuretics* Enteral Nutritional Supplements Gastric Acidity and Peptic Ulcer Agents* Hypnotics* Immunosuppressives	Lipid Lowering Agents Bile Acid-Binding Resins* HMG-CoA reductase Inhibitors* Natural medicines 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* corticotropin cortisone	cyclophosphamide* dicloxacillin ethchlorvynol glutethimide griseofulvin haloperidol meprobamate 6-mercaptopurine methimazole* moricizine hydrochloride* nafcillin paraldehyde pentobarbital	phenobarbital phenytoin* prednisone* primidone propylthiouracil* raloxifene ranitidine* rifampin secobarbital spironolactone sucralfate trazodone vitamin C (high dose) vitamin K warfarin underdosage

also: diet high in vitamin K
unreliable PT determinations

* Increased and decreased PT ratio/INR responses have been reported.

Natural Medicines (Including Herbals and Botanicals)

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

Specific natural medicines reported to affect WARFARIN therapy include the following:

- Bromelains, danshen, dong quai (Angelica sinensis), garlic, and Ginkgo biloba, ginseng, and cranberry products are associated most often with an INCREASE in the effects of WARFARIN. However, the effects of ginseng can be variable (increased or decreased effect of WARFARIN) and the combination should be avoided or more careful monitoring is warranted.
- Coenzyme Q_{10} (ubidecarenome) and St. John's wort are associated most often with a DECREASE in the effects of WARFARIN.

Some natural medicines 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 WARFARIN. Conversely, other natural medicines may have coagulant properties when taken alone or may decrease the effects of WARFARIN.

Some natural medicines that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many natural medicines have several common names and scientific names.

Natural Medicines that contain coumarins with potential anticoagulant effects:	
Agrimony[c] (*Agrimonia eupatoria)*	Horse Chestnut (*Æsculus hippocastanum*)
Alfalfa (*Medicago sativa*)	Horseradish (*Cochleria armoracia*)
Aniseed (*Pimpinella anisum*)	Licorice[c] (*Glycyrrhiza globra*)
Arnica	Meadowsweet[a] (*Spiræa ulmaria*)
Asa Foetida (*Asafetida*)	Nettle (*Urtica dioica*)
Bogbean[a] (*Menyanthis folium*)	Parsley (*Carum petroselinum*)
Peumus Boldo	Passion Flower (*Passiflora edulis*)
Buchu (*Barosmae boldo*)	Prickley Ash – Northern (*Zanthoxylum americanum*)
Paprika (Capsicum)	Quassia (*Amara*)
Cassia[c]	Red Clover (*Trifolium pratense*)
Celery (*Apium graveolens*)	Sweet Clover (*Melilotus officinalis*)
Chamomile–German and Roman (*Anthemis nobilis*)	Sweet Woodruff (*Galii odorati herba*)
Dandelion[c] (*Taraxacum officinale*)	Tonka Beans (*Dipteryx odorata*)
Dong Quai (*Angelica sinensis*)	Wild Carrot (*Daucus carota*)
Fenugreek (*Trigonella fœnumgrœcum*)	Wild Lettuce (*Lactuca virosa*)

Miscellaneous natural medicines with anticoagulant properties:	
Bladder Wrack (Fucus vesiculosus)	Pau d'arco (*Tabebuia avellanedæ*)

Natural medicines that contain salicylate and/or have antiplatelet properties:	
Agrimony[c] (*Argimonia eupatoria*)	Ginger
Aloe Gel	Ginko Biloba
Aspen (*Populus tremuloides*)	Ginseng (Panax)[d]
Black Cohosh (*Cimicifuga racemosa*)	Licorice[c]
Black Haw (*Viburnum prunifolium*)	Meadowsweet[a]
Bogbean[a]	Onion[e] (*Allium cepa*)
Cassia[c]	Policosanol
Clove (*Eugenia caryophyllus*)	Poplar (*Populi gemma*)
Dandelion[c]	Senega (*Polygala*)
Feverfew (*Chrysanthenum parthenum*)	Tamarind (*Tamarindus Indica*)
Garlic[d] (*Tremuloides*)	Willow (*Salix nigra*)
German Sarsaparilla (*Corex arenaria*)	Wintergreen (*Gaultheria procumbens*)

Natural medicines with fibrinolytic properties:	
Bromelains (Bromelainum)	Ginseng (Panax)[d]
Capsicum[b]	Inositol Nicotinate
Garlic[d]	Onion[e]

Natural medicines with coagulant properties:	
Goldenseal (*Chrysanthenum*)	Mistletoe (Viscum album) Yarrow (Achillea millefolium)

[a] Contains coumarins and salicyclate.
[b] Contains coumarins and has fibrinolytic properties.
[c] Contains coumarins and has antiplatelet properties.
[d] Has antiplatelet and fibrinolytic properties.

DOSAGE AND ADMINISTRATION

The administration and dosage of WARFARIN (warfarin sodium) must be individualized according to the patients responsiveness to the drug. The dosage should be adjusted according to results of the patients PT ratio/INR. Measurement of warfarin induced effects on PT can vary substantially due to the sensitivity of different thromboplastin reagents.

Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control 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 best available information supports the following recommendations for dosing of WARFARIN

Venous Thromboembolism (including deep venous thrombosis [DVT] and pulmonary embolism [PE])

For patients with a first episode of DVT or PE secondary to a transient (reversible) risk factor, treatment with warfarin for 3 months is generally recommended. For patients with a first episode of idiopathic DVT or PE, warfarin is generally recommended for at least 6 to 12 months. For patients with two or more episodes of documented DVT or PE, indefinite treatment with warfarin is suggested. For patients with specific risk factors (e.g. documented antiphospholipid antibodies), please refer to current treatment guidelines for recommended duration of treatment.

The dose of warfarin should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations.

Atrial Fibrillation
Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). 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. There are no adequate and well-controlled studies in populations with atrial fibrillation and valvular heart disease. Although clinical studies have used a wide range of warfarin dosing, a more recent study suggests that in patients with atrial fibrillation, anticoagulant prophylaxis is effective at INRs of 2.0 to 3.0. The study also shows that the risk of thromboembolic stroke may increase substantially at INR's less than 2.0. INR value should not exceed 4.0, to reduce the risk of anticoagulant-related bleeding.

Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients. 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 ratio 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 AF patients undergoing elective cardioversion, anticoagulant therapy should be given for three weeks before cardioversion and continued until normal sinus rhythm has been maintained for four weeks.

Oral anticoagulation is recommended in patients with persistent or paroxysmal atrial fibrillation without

valvular disease but at high risk of embolic stroke, i.e., having any of the following features: prior ischemic stroke, transient ischemic attack, or systemic embolism; age >75 years; moderately or severely impaired left ventricular systolic function or congestive heart failure, history of hypertension, or diabetes mellitus. For patients at lower risk, individualized treatment is required. For patients with atrial fibrillation and valvular heart disease, especially mitral valve stenosis, anticoagulation is recommended. For patients with atrial fibrillation and prosthetic heart valves, anticoagulation is required, with the target INR generally increased, with or without acetylsalicylic acid added, depending of risk factors related to the replaced valve or inherent to the patient.

Post-Myocardial Infarction
For most patients following myocardial infarction and not at high risk, antithrombotic treatment should consist of acetylsalicylic acid alone. In patients with acute coronary syndrome that were revascularised by percutaneous coronary intervention (PCI), clopidogrel is usally added. For high-risk patients with myocardial infarction (MI), including those with a large anterior MI, significant heart failure, intracardiac thrombus visible on echocardiography, or those with a history of a thromboembolic event, therapy with combined moderate-intensity warfarin (INR 2.0 to 3.0) plus low-dose acetylsalicylic acid (100 mg/day) for 3 months following myocardial infarction should be considered.

Two well-controlled studies in post-myocardial infarction patients demonstrated substantial benefit of long-term oral anticoagulation in reducing the risk of death, recurrent myocardial infarction, and thromboembolic events, such as stroke. Both studies targeted an INR range of 2.8-4.8 for evaluating efficacy and safety. Clinical evidence from these two studies suggests that an INR range of 2.0-4.0 significantly reduced the risk of thromboembolic events and that INR values greater than 4.0 are associated with an increased risk of bleeding. In post-myocardial patients, WARFARIN therapy should be initiated early and dosage should be adjusted to maintain an INR of 2.5-3.5 long-term. In patients thought to be at increased risk of bleeding complications or on ASA therapy, maintenance of WARFARIN therapy at the lower end of this INR range is recommended.

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy 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.

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

	ISI				
	1	1.4	1.8	2.3	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

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 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 communications 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 IRP, which has an International Sensitivity Index (ISI) of 1.0, were used to perform the test. The INR can be calculated as:

$INR = (\text{observed PT ratio})^{ISI}$ observed PT ratio=(Patient PT/Control PT)

where the ISI is the correction factor in the equation that relates 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.

Recommended Dose and Dosage Adjustment

Initial Dosage

The dosing of WARFARIN must be individualized according to the patients 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. It is recommended that WARFARIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations. The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to WARFARIN. Elderly and Asian patients may require lower initiation and maintenance doses of WARFARIN (see PRECAUTIONS).

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 patients 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 warfarin persists beyond 24 hours. If the patient forgets to take the prescribed dose of WARFARIN 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.

Laboratory Control

The Prothrombin Time (PT) should be determined daily after the administration of the initial dose until International Normalized Ratio (INR) results stabilize in the therapeutic range. Intervals between subsequent INR determinations should be based upon the physician's judgment of the patient's reliability and response to WARFARIN in order to maintain the individual within the therapeutic range. Acceptable intervals for 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 be done when other warfarin products are interchanged with warfarin sodium tablets, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS). Safety and efficacy of warfarin therapy can be improved by increasing the quality of laboratory control. Reports suggest that in usual care monitoring, patients are in therapeutic range only 33%-64% of the time. Time in therapeutic range is significantly greater (56%-93%) in patients managed by anticoagulation clinics.

In switching to another warfarin product, particular emphasis needs to be placed on INR control. INR outside of the therapeutic range may result in serious clinical consequences: lack of efficacy leading to thromboembolic stroke or myocardial infarction, if INR values are low, and intracranial bleeding if they are high.

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 ratio/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 WARFARIN to maintain the PT ratio/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 haemostasis. Under these conditions, dental and surgical procedures may be performed without undue risk of haemorrhage. Some dental or surgical procedures may necessitate the interruption of WARFARIN therapy. When discontinuing WARFARIN even for a short period of time, the benefits and risks should be strongly considered.

Conversion from Heparin Therapy
Since the anticoagulant effect of WARFARIN is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to WARFARIN 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 WARFARIN therapy be overlapped with heparin for 4 to 5 days, until WARFARIN has produced the desired therapeutic response as determined by PT ratio/INR. When WARFARIN has produced the desired PT ratio/INR or prothrombin activity, heparin may be discontinued.

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

As heparin may affect the PT, patients receiving both heparin and WARFARIN should have blood drawn for PT ratio/INR determination, 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 last subcutaneous heparin injection.

OVERDOSAGE

For management of suspected drug overdose, please consult the regional poison control centre.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms:
Suspected or overt abnormal bleeding (e.g., appearance of blood in stools or urine, haematuria, 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 WARFARIN (warfarin sodium) 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 responses to subsequent warfarin therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT. Resumption of warfarin administration reverses the effect of vitamin K_1, and a therapeutic PT 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 haemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of 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 warfarin 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 WARFARIN 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.

ACTION AND CLINICAL PHARMACOLOGY

Warfarin sodium 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. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of g-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 WARFARIN 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

Warfarin sodium 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. It is important that all warfarin sodium products provide the same ratio of enantiomers as that which is present in WARFARIN.

Absorption:

Warfarin is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours. Studies using warfarin sodium indicate the rate but not the extent of absorption of the drug is decreased by the presence of food in the GI tract. Warfarin is also absorbed percutaneously. Individuals differ in the rate at which they absorb warfarin.

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 litre/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. Warfarin is distributed to the liver, lungs, spleen, kidney, and crosses the placenta. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see WARNINGS - Use in Nursing Mothers). Approximately 99% of the drug is bound to plasma proteins.

Metabolism:

Individual patients vary greatly in the rate at which they metabolize warfarin. The elimination of warfarin is almost entirely by metabolism. Warfarin 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 l0-hydroxywarfarin. Numerous cytochrome p-450 isozymes may be involved in the metabolism of warfarin including CYP 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4. CYP 2C9 is likely to be the principal isozyme modulating anticoagulant activity in clinical use. This enzyme constitutes the primary pathway for the metabolism of S-warfarin, the more potent enantiomer found in racemic mixtures of warfarin. Its complete inhibition *in vivo* may be expected to result in lower maintenance dose requirement of warfarin. Individuals with allelic polymorphisms of CYP 2C9 have been identified and have been shown to have lower maintenance dose requirements of warfarin and increased risk of

overanticoagulation.

The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles CYP2C9*2 and CYP2C9*3 result in decreased *in vitro* CYP2C9 enzymatic 7-hydroxylation of S-warfarin. The frequencies of these allelles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively. Patients with one or more of these variant CYP2C9 alleles have decreased S-warfarin clearance (Table 4).

Table 4. Relationship Between S-Warfarin Clearance and CYP2C9 Genotype in Caucasian Patients

CYP2C9 Genotype	N	S-Warfarin Clearance/Lean Body Weight (mL/min/kg) Mean (SD)[a]
*1/*1	118	0.065 (0.025)[b]
*1/*2 or *1/*3	59	0.041 (0.021)[b]
*2/*2, *2/*3 or *3/*3	11	0.020 (0.011)[b]
Total	188	

[a]SD=standard deviation.
[b]p<0.001. Pairwise comparisons indicated significant differences among all 3 genotypes.

Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9 and *11 alleles in Caucasians.

Pharmacogenomics

A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients. In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements. The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles. Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele. For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele.

In an observational study, the risk of achieving INR >3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype. The relative risk of over anticoagulation as measured by INR >3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele.

Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin. In 201 Caucasian patients treated with stable warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses. In this study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in VKORC1 and CYP2C9 genes combined. About 55% of the variability in warfarin dose could be explained by the combination of

VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients. Similar observations have been reported in Asian patients.

Elimination:

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.

In the Elderly

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulation effects of warfarin. The cause of this increased sensitivity in this age group is not known. This increased anticoagulat effect of 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 suggest that there is no difference in the clearance of S-warfarin in the elderly, compared to that seen in young subjects. However, there may be slight decrease in the clearance of R-warfarin in the elderly, compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

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

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

STORAGE AND STABILITY

Stability and Storage Recommendations:
Protect from light. Store at room temperature (15°C to 30°C). Dispense in a tight, light-resistant container as defined in the USP.

SPECIAL HANDLING INSTRUCTIONS
Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:
WARFARIN (warfarin sodium) tablets contain the following ingredients: Corn Starch, Lactose Monohydrate, Stearic Acid, Magnesium Stearate and colour dye which varies in each tablet strength.

1 mg:	FD&C Red #40 Aluminum Lake
2 mg :	FD&C Red #40 Aluminum Lake
	FD&C Blue #2 Aluminum Lake

2.5 mg:	FD&C Blue #1 Aluminum Lake HT
	D&C Yellow #10 Aluminum Lake
3 mg:	FD&C Blue No. 2 Aluminum Lake
	FD&C Yellow No. 6 Aluminum Lake
	FD&C Red No. 40 Aluminum Lake
4 mg :	FD&C Blue #1 Aluminum Lake
5 mg :	FD&C Yellow #6 Aluminum Lake
6 mg:	FD & C Blue No. 1 Aluminum Lake
	FD & C Yellow No. 6 Aluminum Lake
7.5 mg:	FD&C Yellow #6 Aluminum Lake
	D&C Yellow #10 Aluminum Lake
10 mg:	Dye free

AVAILABILITY OF DOSAGE FORMS

WARFARIN (warfarin sodium) tablets are single-scored and imprinted as follows:

Strength	Imprint Side 1	Imprint Side 2	Colour
1 mg	WF / 1	G	Dark Pink
2 mg	WF / 2	G	Lavender
2.5 mg	WF / 2.5	G	Green
3 mg	WF / 3	G	Brown
4 mg	WF / 4	G	Blue
5 mg	WF / 5	G	Peach
6 mg	WF / 6	G	Greenish-Blue
7.5 mg	WF / 7.5	G	Yellow
10 mg	WF / 10	G	White

Supplied in Bottles of 100 and 1000 tablets for 1 mg, 2 mg, 2.5 mg and 5 mg strengths, and Bottles of 100 tablets for 3 mg, 4 mg, 6 mg, 7.5 mg and 10 mg strengths.

PART II: SCIENTIFIC INFORMATION

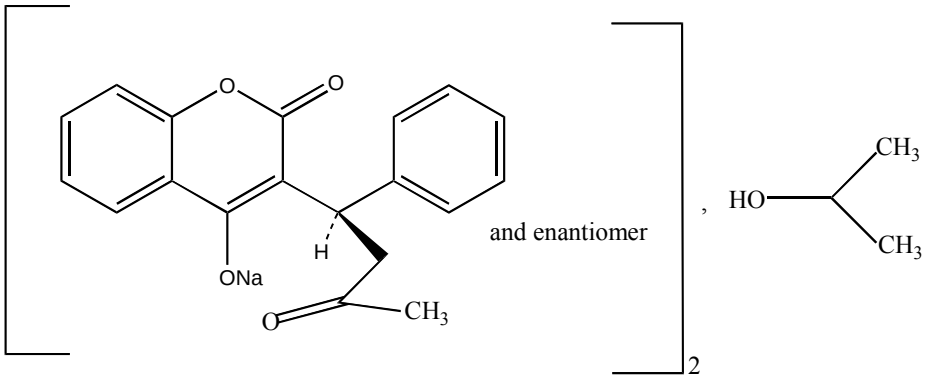
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Warfarin Sodium, USP (crystalline clathrate)

Chemical Name: 3-(α-acetonyl-benzyl)-4-hydroxycoumarin sodium salt x ½ isopropyl alcohol

Structural Formula:



Molecular Formula: $C_{19}H_{15}NaO_4$ x $½C_3H_8O$ (crystalline clathrate)

Molecular Weight: 360.37 g/mol (crystalline clathrate)

Molecular Formula: $C_{19}H_{15}NaO_4$ (anhydrous and isopropyl-free molecule)

Molecular Weight: 330.31 (anhydrous and isopropyl-free molecule)

Description:
Warfarin sodium occurs as a white, odourless, crystalline powder which has a slightly bitter taste, is discoloured by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

pH: Between 7.2 and 8.3, in a solution (1 in 100).

Melting Point: Between 157°-167°C, range not to exceed 4°C.

pKa: 5.05.

CLINICAL TRIALS

Comparative Bioavailability Studies

Four randomized, double-blinded, two-way, single-dose, cross over, bioavailability studies were performed. Two were fasted studies while the other two were fed studies. One fasted and one fed study was done using the 2 mg strength while the second fasted and the second fed study was performed on the 10 mg strength. All studies compared WARFARIN against the Canadian Reference Product Coumadin®. The pharmacokinetic data is presented below.

TABLE: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR WARFARIN SODIUM
(2x2mg) Under Fasted Conditions From Measured Data

PARAMETER	Geometric Mean Arithmetic Mean (C.V.)		% RATIO OF GEOMETRIC MEANS	95% GEOMETRIC CONFI-DENCE INTERVAL
	TEST (WARFARIN)	REFERENCE (Coumadin®)		
AUC_{0-72} (ng.h/mL)	11581.93 11839.11 (21.14%)	12154.58 12414.06 (20.83%)	95%	88 - 103%
AUC_{0-t} (ng.h/mL)	14479.90 14768.22 (20.61%)	14680.83 14941.83 (19.08%)	99%	94 - 104%
AUC_I (ng.h/mL)	20660.55 21240.12 (26.04%)	20970.55 21671.72 (26.74%)	99%	93 - 105%
C_{MAX} (ng/mL)	487.977 497.87 (20.21%)	492.436 508.53 (26.65%)	99%	89 - 110%
T_{MAX}* (h)	1.21 (87.29%)	1.07 (105.1%)	-	
$T_{½}$* (h)	56.18 (17.96%)	56.68 (20.87%)	-	

* expressed as arithmetic mean (CV%) only.
Coumadin® manufactured by Dupont Merck Pharma Inc.

TABLE: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR WARFARIN SODIUM
(2x2mg) Under Fed Conditions From Measured Data

PARAMETER	**Geometric Mean Arithmetic Mean (C.V.)**		% RATIO OF GEOMETRIC MEANS	95% GEOMETRIC CONFIDENCE INTERVAL
	TEST (WARFARIN)	**REFERENCE (Coumadin®)**		
AUC_{0-72} (ng.h/mL)	11951.59 12259.27 (23.13%)	12406.31 12560.21 (15.92%)	96%	91 - 102%
AUC_{0-t} (ng.h/mL)	14144.55 14487.61 (22.51%)	14795.08 15019.46 (17.59%)	96%	92 - 99%
AUC_I (ng.h/mL)	19132.63 19616.00 (23.51%)	19904.46 20402.65 (22.53%)	96%	93 - 99%
C_{MAX} (ng/mL)	379.124 386.61 (20.39%)	389.178 393.61 (15.49%)	97%	91 - 104%
T_{MAX}* (h)	3.07 (28.92%)	2.67 (40.14%)	-	
$T_{½}$* (h)	51.14 (23.45%)	49.74 (17.12%)	-	

* expressed as arithmetic mean (CV%) only.
Coumadin® manufactured by Dupont Merck Pharma Inc.

TABLE: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR WARFARIN SODIUM
(1x10mg) Under Fasted Conditions From Measured Data

PARAMETER	Geometric Mean Arithmetic Mean (C.V.)		% RATIO OF GEOMETRIC MEANS	95% GEOMETRIC CONFIDENCE INTERVAL
	TEST (WARFARIN)	REFERENCE (Coumadin®)		
AUC_{0-72} (ng.h/mL)	42823.39 43637.32 (21.08%)	40307.53 41157.33 (22.21%)	106%	100 - 113 %
AUC_{0-t} (ng.h/mL)	50171.26 51442.75 (26.11%)	47192.43 48171.40 (22.52%)	106%	102 - 110 %
AUC_I (ng.h/mL)	64047.38 66651.07 (32.49%)	61123.37 63313.40 (29.84%)	105%	101 - 109 %
C_{MAX} (ng/mL)	1579.54 1629.30 (29.06%)	1618.00 1663.34 (26.74%)	98%	89 - 107 %
T_{MAX}* (h)	1.62 (77.62%)	1.07 (48.29%)	–	
$T_{½}$* (h)	43.78 (21.51%)	45.92 (24.96%)	–	

* expressed as arithmetic mean (CV%) only.
Coumadin® manufactured by Dupont Merck Pharma Inc.

TABLE: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR WARFARIN SODIUM
(1x10mg) Under Fed Conditions From Measured Data

PARAMETER	Geometric Mean Arithmetic Mean (C.V.)		% RATIO OF GEOMETRIC MEANS	95% GEOMETRIC CONFIDENCE INTERVAL
	TEST (WARFARIN)	REFERENCE (Coumadin®)		
AUC_{0-72} (ng.h/mL)	44236.44 45995.10 (27.55%)	42668.07 43914.79 (24.46%)	104%	99 - 108 %
AUC_{0-t} (ng.h/mL)	53733.95 55850.49 (27.38%)	51602.33 52952.75 (22.97%)	104%	100 - 109 %
AUC_I (ng.h/mL)	71463.22 76614.22 (39.56%)	67301.82 70879.96 (34.61%)	106%	100 - 113 %
C_{MAX} (ng/mL)	1278.41 1304.00 (20.79%)	1300.25 1339.80 (23.83%)	98%	92 - 105 %
T_{MAX}^* (h)	3.78 (30.37%)	3.70 (61.81%)	-	
$T_{½}^*$ (h)	47.72 (29.14%)	45.70 (32.75%)	-	

* expressed as arithmetic mean (CV%) only.
Coumadin® manufactured by Dupont Merck Pharma Inc.

TOXICOLOGY

Carcinogenicity and mutagenicity studies have not been performed with warfarin sodium. The reproductive effects of warfarin have not been evaluated.

Warfarin is contraindicated in women who are or who may become pregnant because the drug passes through the placental barrier and may cause fatal haemorrhage 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 (see CONTRAINDICATIONS).

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PART III: CONSUMER INFORMATION

Pr WARFARIN
(Warfarin Sodium)

This leaflet is part III of a three-part "Product Monograph" published when WARFARIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about WARFARIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- **WARFARIN** is an anticoagulant drug. "Anti" means against, and "coagulant" refers to blood clotting. An anticoagulant helps reduce clots from forming in the blood.
- **WARFARIN** is a narrow therapeutic index drug, which means that there is a narrow margin between too much and too little of the drug. Too much drug may cause you to bleed more. Too little drug may let a harmful clot form.

What it does:

See What the medication is used for.

- **WARFARIN** partially blocks the re-use of vitamin K in your liver. Vitamin K is needed to make clotting factors that help the blood to clot and prevent bleeding. Vitamin K is found naturally in foods such as leafy, green vegetables and certain vegetable oils.
- **WARFARIN** begins to reduce blood clotting within 24 hours after taking the drug. The full effect may take 72 to 96 hours to occur. The anti-clotting effects of a single dose of **WARFARIN** last 2 to 5 days, but it is important for you to take your dose every day.

When it should not be used:

- Do not take **WARFARIN** during pregnancy. Use effective measures to avoid pregnancy while taking **WARFARIN**.
- Do not start, stop, or change any medicine except on advice of your health care provider.
- Do not make drastic changes in your diet, such as eating large amounts of green, leafy vegetables. The amount of vitamin K in your daily diet may affect therapy with WARFARIN.
- Do not attempt to change your weight by dieting, without first checking with your health care provider.
- Avoid alcohol consumption.
- Do not participate in any activity or sport that may result in serious injury.
- Avoid cutting yourself.

What the medicinal ingredient is:

Warfarin Sodium

What the nonmedicinal ingredients are:

Corn Starch, Lactose Monohydrate, Stearic Acid, Magnesium Stearate and colour dye which varies in each tablet strength.

1 mg:	FD&C Red #40 Aluminum Lake
2 mg :	FD&C Red #40 Aluminum Lake
	FD&C Blue #2 Aluminum Lake
2.5 mg:	FD&C Blue #1 Aluminum Lake HT
	D&C Yellow #10 Aluminum Lake
3 mg:	Lake Blend Brown LB-1685
4 mg :	FD&C Blue #1 Aluminum Lake
5 mg :	FD&C Yellow #6 Aluminum Lake
6 mg:	Lake Blend Dark Green LB-1236
7.5 mg:	FD&C Yellow #6 Aluminum Lake
	D&C Yellow #10 Aluminum Lake
10 mg:	Dye free

What dosage forms it comes in:

WARFARIN tablets are available in 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg strengths.

WARNINGS AND PRECAUTIONS

What should I tell my healthcare provider before starting WARFARIN

Tell your healthcare provider about all of your health conditions, including if you:

- have bleeding problems
- fall often
- have liver or kidney problems
- have high blood pressure
- have a heart problem called congestive heart failure
- have diabetes
- drink alcohol or have problems with alcohol abuse. Alcohol can affect your WARFARIN dose and should be avoided.
- are pregnant or planning to become pregnant.
- are breastfeeding. WARFARIN may increase bleeding in your baby. Talk to your doctor about the best way to feed your baby. If you choose to breastfeed while taking WARFARIN, both you and your baby should be carefully monitored for bleeding problems.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

- Like all prescription drugs, **WARFARIN** may cause side effects. The most common side effect of **WARFARIN** is bleeding, which may be serious. However, the risk of serious bleeding is low when the effect of **WARFARIN** is within a range that is right for your specific medical condition. Notify your health care provider right away of any unusual bleeding or if signs or symptoms of bleeding occur.
- Do not take **WARFARIN** during pregnancy, Use effective measures to avoid pregnancy while taking **WARFARIN**.
- The dose of **WARFARIN** may be different for each patient. For example, older patients (age 60 years of age or older) appear to have a greater-than-expected response to **WARFARIN** so that as patient age increases, a lower dose of **WARFARIN** may be needed. Your health care provider will decide what dose is best for you. This dose may change from time to time.
- To decide on the dosage of **WARFARIN** you need, your health care provider will take a small amount of your blood to find out your prothrombin time, protime,

or PT, for short. Protimes are often recorded as an INR (International Normalized Ratio), a standard way of reporting protimes.

- PT/INR tests are very important. They help your health care provider see how fast your blood is clotting and whether your dosage of **WARFARIN** should change.
- When you start taking **WARFARIN**, you may have PT/INR tests every day for a few days, then perhaps one time every week. **These PT/INR tests and regular visits to a health care provider are very important for the success of therapy with WARFARIN**. PT/INR tests will be needed at periodic intervals (such as one time per month) throughout your course of therapy to keep your PT/INR in the best range for your medical condition. Discuss with your health care provider the range that is right for you.
- A severe elevation (> 50 seconds) in activated partial thromboplastin time (aPTT) with a PT ration/INR in the desired range has been identified as an indication of increased risk of postoperative haemorrhage. This has been noted in patients undergoing elective hip surgery receiving warfarin alone.
- Eat a normal balanced diet maintaining a consistent level of green, leafy vegetables that contain high amounts of Vitamin K since the amount of vitamin K in your daily diet may affect **WARFARIN** therapy.
- Report any illness, such as throwing up (vomiting), loose or runny stools (diarrhea), an infection or fever, to your health care provider.
- Tell anyone giving you medical or dental care that you are taking **WARFARIN**.
- Carry identification stating that you are taking **WARFARIN**.
- Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your healthcare provider may need to check you.
- Tell your healthcare provider about any planned surgeries, medical or dental procedures. Your **WARFARIN** may have to be stopped for a short time or you may need your dose adjusted.

INTERACTIONS WITH THIS MEDICATION

WARFARIN interacts with many different drugs, including acetylsalicylic acid and acetylsalicylic acid-containing ointments and skin creams as well as natural medicines (e.g., bromelains, coenzyme Q_{10}, danshen (Colocasia antiquorum), dong quai (Angelica sinensis), garlic, ginkgo biloba, ginseng and St. John's wort). Tell your health care provider about any prescription and non-prescription (over-the-counter) drugs that you are taking including occasional use of headache medications. Avoid cranberry juice or other cranberry products while taking **WARFARIN**. For more details refer to WARNINGS and PRECAUTIONS section, above.

PROPER USE OF THIS MEDICATION

Please read this leaflet before you start taking **WARFARIN** (warfarin sodium). Each time you renew your prescription, read the leaflet that comes with your medicine, just in case any information has changed. Remember, this leaflet does not take the place of talking to your health care provider (such as your doctor, nurse, or pharmacist). You and your health care provider should discuss **WARFARIN** when you start taking your medication and at regular checkups.

- Take **WARFARIN** exactly the way your health care provider tells you and take it at the same time every day. You can take **WARFARIN** either with food or on an empty stomach. Your dosage may change from time to time depending on your response to **WARFARIN**.

Overdose:
In case you have taken too much WARFARIN, contact your doctor, regional poison control centre or local hospital. Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing WARFARIN (warfarin sodium) therapy and if necessary, by administration of oral or parenteral vitamin K_1. In case you have taken too much WARFARIN, contact your doctor, regional poison control centre or local hospital.

Missed Dose:

- If you miss a dose of **WARFARIN**, notify your health care provider right away. Take the dose as soon as possible on the same day, but do not take a double dose of **WARFARIN** the next day to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Your health care provider can tell you about possible side effects of **WARFARIN**, which include bleeding and allergic reactions. To lower the risk of bleeding, your PT/INR should be kept within a range that is right for you.

Please contact your health care provider right away if you experience any of the following signs or symptoms of bleeding problems.

- headache, dizziness, or weakness
- bleeding from shaving or other cuts that does not stop
- nosebleeds
- bleeding of gums when brushing your teeth
- coughing up blood
- vomiting blood or material that looks like coffee grounds
- unusual bruising (black-and-blue marks on your skin) for unknown reasons
- pink or dark brown urine
- red or black color in your stool
- more bleeding than usual when you get your menstrual period or unexpected bleeding from the vagina
- unusual pain or swelling

Serious, but rare, side effects of **WARFARIN** include skin necrosis (death of skin tissue) and "purple toe syndrome," either of which may require removal of unhealthy tissue and/or amputation of the affected area. Call your healthcare provider right away if you have pain, color, or temperature change to any area of your body or if you have pain in your toes and they look purple or dark in color. You may need medical care right away.

Talk with your health care provider for further information on these side effects.

Hypersensitivity/allergic reactions are reported infrequently. Signs or symptoms of these reactions may range from mild reactions (rash, itching, hives) to more severe reactions (trouble breathing, throat tightening or constriction, facial swelling, swollen lips or tongue, sudden low blood pressure).

These are not all of the side effects of WARFARIN. For more information, ask your healthcare provider or pharmacist.

HOW TO STORE IT

As with all medicines, keep **WARFARIN** out of the reach of children.

Protect from light. Store at room temperature (15 °C to 30 °C).

Keep the container tightly closed.

There is an expiry date on the label. Do not use the medicine after this date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  -Fax toll-free to 1-866-678-6789, or
  -Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sanis Health Inc., at:
Phone: 1-866-236-4076;
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