

Product Monograph
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr} **TARO-WARFARIN**

Warfarin Sodium Tablets, USP

1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg Immediate Release Tablets

ANTICOAGULANT

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PRODUCT MONOGRAPH

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ANTICOAGULANT

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 K₁ 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 Taro-Warfarin (warfarin sodium) tablets.

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 Sodium 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. 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 alleles 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 1).

Table 1. 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	

^aSD=standard deviation.

^bp<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.

Geriatric Patients

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 anticoagulant 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 a 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.

Renal Impairment

Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin.

Hepatic Impairment

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

Bioequivalence Studies

Four bioavailability studies were performed in order to establish bioequivalence between TARO-WARFARIN tablets and the brand product. The results of the studies are summarized in the tables below:

Two-way, Crossover, Single Dose, Food-Effect Study
TARO-WARFARIN (Warfarin Sodium) Tablets USP, 10 mg
Immediate Release Tablets

Warfarin Sodium Tablets (1 x 10 mg)
Warfarin (from measured data)

Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TARO-WARFARIN 10 mg tablets (Taro Pharmaceuticals)	COUMADIN®* 10 mg tablets (DuPont Pharma, Canada)	RATIO OF MEANS 95% CI (80 - 125%)
AUC ₀₋₇₂ (ng hr/mL)	37681 37672 (15%)	36783 37252 (13%)	102 (98-107)
AUC _{0-T} (ng hr/mL)	46187 46241 (17%)	45075 45761 (14%)	102 (98-108)
AUC _{0-inf} (ng hr/mL)	52257 52396 (18%)	51166 52153 (16%)	102 (97-108)
C _{max} (ng/mL)	1099 1097 (14%)	1098 1105 (10%)	100 (95-105)
T _{max} (hr)	3.14 (44%)	3.32 (41%)	-----
T _{1/2} (hr)	38.4 (15%)	39.4 (13%)	-----

for T_{max} and T_{1/2} arithmetic mean (CV%) are presented

*Purchased in Canada

Two-way, Crossover, Single Dose, Fasting Study
TARO-WARFARIN (Warfarin Sodium) Tablets USP, 10 mg
Immediate Release Tablets

Warfarin Sodium Tablets (1 x 10 mg)
Warfarin (from measured data)

Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TARO-WARFARIN 10 mg tablets (Taro Pharmaceuticals)	COUMADIN®* 10 mg tablets (DuPont Pharma Canada)	RATIO OF MEANS 95% CI (80 - 125%)
AUC ₀₋₇₂ (ng hr/mL)	38280 39699 (21%)	38226 39649 (19%)	100 (96-104)
AUC _{0-t} (ng hr/mL)	47345 49260 (26%)	47038 48854 (20%)	101 (97 - 105)
AUC _{0-inf} (ng hr/mL)	55467 59145 (41%)	54870 57558 (26%)	101 (96 - 106)
C _{max} (ng/mL)	1324 1387 (17%)	1416 1481(20%)	94 (87 - 100)
T _{max} (hr)	1.78 (186 %)	1.17 (88%)	-----
T _{1/2} (hr)	44.0 (28%)	43.8 (23%)	-----

for T_{max} and T_{1/2} arithmetic mean (CV%) are presented

*Purchased in Canada

Two-way, Crossover, Single Dose, Fasting Study
TARO-WARFARIN (Warfarin Sodium) Tablets, 1 mg
Immediate Release Tablets

Warfarin Sodium Tablets (2 x 1 mg)
Warfarin (from measured data)

Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TARO-WARFARIN 2 x 1 mg tablets (Taro Pharmaceuticals)	COUMADIN®* 2 x 1 mg tablets (DuPont Pharma Canada)	% RATIO OF MEANS 95% CI (80-125%)
AUC _{0-72h} (ng.hr/mL)	4716.72 4876.27 (24.33%)	4563.34 4667.06 (21.50%)	103.36 (96.29 - 110.96)
AUC _{0-inf} (ng.hr/mL)	8305.53 8773.99 (32.83%)	8234.22 8504.53 (27.34%)	100.87 (91.76 - 110.88)
C _{max} (ng/mL)	234.9 240.19 (20.71%)	239.21 244.99 (24.20%)	98.19 (90.48 - 106.56)
T _{max} (hr)	0.548 (23.36%)	0.667 (104.28%)	-----
T _{1/2 el} (hr)	63.29 (25.86%)	64.27 (27.92%)	-----

for T_{max} and T_{1/2} arithmetic mean (CV%) are presented

*Purchased in Canada

Two-way, Crossover, Single Dose, Fed Study
TARO-WARFARIN (Warfarin Sodium) Tablets, 1 mg
Immediate Release Tablets

Warfarin Sodium Tablets (2 x 1 mg)
Warfarin (from measured data)

Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TARO-WARFARIN 2 x 1 mg tablets (Taro Pharmaceuticals)	COUMADIN®* 2 x 1 mg tablets (DuPont Pharma Canada)	% RATIO OF MEANS 95% CI (80-125%)
AUC _{0-72h} (ng.hr/mL)	4691.52 4895.45 (29.03%)	4731.91 5012.25 (25.46%)	99.15 (95.70 - 102.72)
AUC _{0-inf} (ng.hr/mL)	9234.38 9677.56 (34.18%)	8933.19 9500.91 (31.56%)	103.37 (95.10 - 112.37)
C _{max} (ng/mL)	141.45 143.99 (20.34%)	146.68 151.73 (22.69%)	96.43 (89.37 - 104.05)
T _{MAX} * (hr)	2.47 (57.29%)	2.35 (55.53%)	-----
T _{1/2 el} * (hr)	71.85 (25.95%)	67.16 (25.30%)	-----

for T_{max} and T_{1/2} arithmetic mean (CV%) are presented

*Purchased in Canada

INDICATIONS AND CLINICAL USE

TARO-WARFARIN (warfarin sodium) tablets are 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 and 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

TARO-WARFARIN (warfarin sodium) tablets are 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 TARO-WARFARIN Tablet 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. central nervous system haemorrhage
3. cerebral aneurysms or dissecting aorta
4. pericarditis and pericardial effusions
5. bacterial endocarditis

Threatened abortion, eclampsia and preeclampsia

Inadequate laboratory facilities

Unsupervised patients with conditions associated with potential high level of noncompliance such as senility, alcoholism, or psychosis or other lack of patient cooperation.

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

Miscellaneous

Hypersensitivity to warfarin sodium or to any other components of TARO-WARFARIN Tablets.

Major regional or lumbar block anesthesia.

Malignant hypertension.

WARNINGS

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 appropriate for the clinical condition. However, maintenance of INR in the therapeutic range does not eliminate the risk of bleeding. Drugs, dietary changes, and other factors affect INR levels achieved with Taro-Warfarin therapy. Perform more frequent INR monitoring when starting or stopping other drugs, including botanicals, or when changing dosages of other drugs. 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)

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 pathological bleeding.

Haemorrhage

The most serious risk associated with anticoagulant therapy with TARO-WARFARIN (warfarin sodium) tablets is haemorrhage in any tissue or organ (see WARNING BOX). The risk of haemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Haemorrhage has in some cases been reported to result in death or permanent disability.

Tissue Necrosis

Necrosis and/or gangrene of skin and other tissues is an uncommon but serious risk (<0.1%). It may be associated with local thrombosis and usually appears within a few days of the start of TARO-WARFARIN therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Necrosis has in some cases been reported to result in death or permanent disability.

Careful clinical evaluation 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. Discontinue TARO-WARFARIN therapy if necrosis occurs. Consider alternative drugs if continued anticoagulation therapy is necessary.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. TARO-WARFARIN Tablets, 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 TARO-WARFARIN Tablets are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Drugs, dietary changes, and other factors affect INR levels achieved with TARO-WARFARIN therapy. Perform more frequent INR monitoring when starting or stopping other drugs, including botanicals, or when changing dosages of other drugs (see Drug Interactions).

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

Use in Patients with altered glomerular integrity

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and hematuria (see WARNINGS - Special Population: Renal Impairment; DOSE AND ADMINISTRATION - Renal Impairment).

Calciphylaxis

Calciphylaxis, also known as calcific uremic arteriolopathy, has been reported in predisposed patients, mainly end-stage renal disease (ESRD) patients under dialysis, but also patients with known risk factors such as hyperphosphatemia, hypercalcemia, low serum albumin levels or receiving vitamin K antagonists, including warfarin. When calciphylaxis is diagnosed in these patients, discontinue TARO-WARFARIN, start specific calciphylaxis supportive treatments, and consider if continued alternative anticoagulation therapy is necessary.

Systemic atheroemboli and cholesterol microemboli

Anticoagulation therapy with TARO-WARFARIN Tablets may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toe syndrome". 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 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. Discontinue TARO-WARFARIN therapy if such phenomena are observed. Consider alternative drugs if continued anticoagulation therapy is necessary.

Purple toe syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color 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 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.

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 impairment 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. Deficiency in protein C-mediated anticoagulant response: TARO-WARFARIN reduces the synthesis of the naturally occurring anticoagulants, protein C and protein S. 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 sodium tablets 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. Eye surgery: In cataract surgery, Warfarin tablets use was associated with a significant increase in minor complications of sharp needle and local anesthesia block, but not associated with potentially sight-threatening operative hemorrhagic complications. As Warfarin tablets cessation or reduction may lead to serious thromboembolic complications, the decision to discontinue TARO-WARFARIN before a relatively less invasive and complex eye surgery, such as lens surgery, should be based upon the risks of anticoagulant therapy weighed against the benefits.
9. Diseases affecting the microvasculature or microcirculation, such as polycythemia vera,

- vasculitis, and severe diabetes.
10. Poor nutritional state.
 11. Vitamin K deficiency.
 12. Increased vitamin K intake.
 13. Hereditary warfarin resistance.

Heparin-Induced Thrombocytopenia

Do not use TARO-WARFARIN as initial therapy in patients with heparin-induced thrombocytopenia (HIT) and with heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Cases of limb ischemia, necrosis, and gangrene have occurred in patients with HIT and HITTS 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. Treatment with TARO-WARFARIN may be considered after the platelet count has normalized.

Special Populations

Renal impairment

Patients with renal impairment who are taking warfarin should be instructed to be more vigilant in monitoring their INR (see Renal Impairment).

Pregnancy

In humans, warfarin crosses the placenta, and concentrations in fetal plasma approach the maternal values and may cause fatal haemorrhage to the fetus *in utero*. Exposure to warfarin during the first trimester of pregnancy caused a pattern of congenital malformations in about 5% of exposed offspring. Warfarin embryopathy is characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) and growth retardation (including low birth weight). Central nervous system and eye abnormalities have also been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, midline cerebellar atrophy, and ventral midline dysplasia characterized by optic atrophy. Mental retardation, blindness, schizencephaly, microcephaly, hydrocephalus, and other adverse pregnancy outcomes have been reported following warfarin exposure during the second and third trimesters of pregnancy (See CONTRAINDICATIONS).

Use in Nursing Mothers

Based on published data in 15 nursing mothers, warfarin was not detected in human milk. Among the 15 full-term newborns, 6 nursing infants had documented prothrombin times within the expected range. Prothrombin times were not obtained for the other 9 nursing infants. Monitor breastfeeding infants for bruising or bleeding. Effects in premature infants have not been evaluated. Caution should be exercised when TARO-WARFARIN is administered to a nursing woman. 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.

Treatment during dentistry and surgery

Some dental or surgical procedures may necessitate the interruption or change in the dose of TARO-WARFARIN therapy. Consider the benefits and risks when discontinuing TARO-WARFARIN even for a short period of time. Determine the INR immediately prior to any dental or surgical procedure. In patients undergoing minimally invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of TARO-WARFARIN to maintain the INR at the low end of the therapeutic range may safely allow for continued anticoagulation.

Miscellaneous:

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 sodium tablets have been reported. Exaggerated therapeutic responses have been reported in other patients.

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

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 ratio/INR or other suitable coagulation test is essential (see DOSAGE AND ADMINISTRATION: Laboratory Control).

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 including warfarin. It is generally good practice to monitor the patient's 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. This includes drugs intended for short-term use (eg, antibiotics, antifungals, corticosteroids). The following tables in this section provide a listing of factors, alone or in combination, which may affect the PT. However, other factors may also affect the anticoagulant response and the tables are provided for your reference only.

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

Because a patient may be exposed to a combination of listed factors, the net effect of warfarin sodium tablets on PT ratio/INR responses may be unpredictable. More frequent PT/INR monitoring should be performed when starting or stopping other drugs, including botanicals, or when changing dosages of other drugs, including drugs intended for short-term use (eg, antibiotics, antifungals, corticosteroids).

Consult the labeling of all concurrently used drugs to obtain further information about interactions with COUMADIN or adverse reactions pertaining to bleeding.

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

Drug Interactions

Drug Interactions Overview

CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. The more potent warfarin S-enantiomer (60% of the overall anticoagulation response) is metabolized by CYP2C9 while the R-enantiomer is metabolized by CYP1A2 and 3A4. The steady state concentration of warfarin is mediated by CYP2C9 mediated metabolism of S-enantiomer .

- Inhibitors of CYP2C9, 1A2, and/or 3A4 have the potential to increase the effect (increase INR) of warfarin by increasing the exposure of warfarin.
- Inducers of CYP2C9, 1A2, and/or 3A4 have the potential to decrease the effect (decrease INR) of warfarin by decreasing the exposure of warfarin.

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

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.

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

Table 2 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Nonsteroidal antiinflammatory drugs (NSAIDs)	C, CT	May affect prothrombin time. May inhibit platelet aggregation. May cause gastrointestinal bleeding, peptic ulceration and/or perforation. May increase bleeding risk.	Close monitoring of patients receiving nonsteroidal anti-inflammatory agents (NSAIDs) is recommended to be certain that no change in anticoagulation dosage is required. Bleeding risk is increased when these drugs are used concomitantly with warfarin. Adjust dosage accordingly or discontinue if necessary. Consult the labeling of all concurrently used drugs to obtain further information about interactions with TARO-WARFARIN or adverse reactions pertaining to bleeding.
Anticoagulants Platelet antiaggregants Thrombolytics Serotonin reuptake inhibitors	CT CT C CT	May increase bleeding risk.	Bleeding risk is increased when these drugs are used concomitantly with warfarin, closely monitor patients receiving any such class of drug with TARO-WARFARIN. Adjust dosage accordingly or discontinue if necessary.
Antibiotics and antifungals	CT	May change international normalized ratio (INR).	There have been reports of changes in INR in patients taking warfarin and antibiotics or antifungals, but clinical pharmacokinetic studies have not shown consistent effects of these agents on plasma concentrations of warfarin. Coadministration with warfarin should be avoided or closely monitor INR when starting or stopping any antibiotic or antifungal in patients taking TARO-WARFARIN.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

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

Table 3. ENDOGENOUS FACTORS:

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

Table 4. EXOGENOUS FACTORS:

Potential drug interactions with TARO-WARFARIN are listed below by drug class and by specific drugs.

Classes of Drugs

5-lipoxygenase Inhibitors	Adrenergic Stimulants, Central Alcohol Abuse Reduction Preparations	Analgesics
Anaesthetics, Inhalation	Antiandrogens	Antiarrhythmics *
Antibiotics * Aminoglycosides (oral) Cephalosporins (parenteral) Macrolides Penicillins (intravenous), high dose Quinolones (fluoroquinolones) Sulfonamides (long acting) Tetracyclines	Anticoagulants	Anticonvulsants *
Antidepressants *	Anti-fungal Medications, Intravaginal, Systemic*	Antimalarial Agents
Antineoplastics*	Antiparasitic/Antimicrobials	Antiplatelet Drugs/Effects
Antithyroid Drugs *	Beta-Adrenergic Blockers	Cholelitholytic Agents
Diabetes Agents, Oral Diuretics *	Gastric Acidity and Peptic Ulcer Agents *	Gastrointestinal, Ulcerative Colitis Agents
Gastrointestinal, Prokinetic Agents	Gout Treatment Agents	Hemorrhologic Agents
Hepatotoxic Drugs	Hyperglycemic Agents	Hypertensive Emergency Agents
Hypnotics *	Leukotriene Receptor Antagonists	Lipid Lowering Agents* Bile Acid-Binding Resins* Fibrates HMG-CoA Reductase

		Inhibitors*
Monoamine Oxidase Inhibitors	Narcotics, prolonged	Natural medicines
Nonsteroidal Anti-Inflammatory Agents Cox-2 Inhibitors Nonselective NSAIDS	Psychostimulants	Pyrazolones
Salicylates	Selective Serotonin Reuptake Inhibitors	Steroids, Adrenocortical *
Steroids, Anabolic (17-Alkyl Testosterone Derivatives)	Thrombolytics	Thyroid Drugs
Tuberculosis Agents *	Uricosuric Agents	Vaccines
Vitamins *		

Table 5. Specific Drugs with potential interactions with TARO-WARFARIN

Acetaminophen (paracetamol)	alcohol*	allopurinol	aminosalicylic acid	amiodarone HCl
amoxicillin	argatroban	ASA (acetylsalicylic acid)	azithromycin	bezafibrate
Benzbromarone	benziodarone	bivalirudin	capecitabine	carboplatin
cefaclor	cefamandole	cefazolin	cefixime	cefonicid
cefoperazone	cefotetan	cefotiam	cefoxitin	ceftriaxone
cefuroxime	celecoxib	chenodiol	chloramphenicol	chloral hydrate*
chlorpropamide	cholestyramine*	cimetidine	ciprofibrate	ciprofloxacin
cisapride	citalopram	clarithromycin	clofibrate	COUMADIN overdose
cyclophosphamide*	danazol	danshen (Chinese herb)	desirudin	dextran
dextrothyroxine	diazoxide	diclofenac	dicumarol	diflunisal
disulfiram	doxycycline	econazole	erythromycin	escitalopram
esomeprazole	ethacrynic acid	ezetimibe	fenofibrate	fenoprofen
fluconazole	fluorouracil	fluoxetine	flutamide	fluvastatin
flvoxamine	gatifloxacin	gefitinib	gemfibrozil	glucagon
glucosamine	halothane	heparin	ibuprofen	ifosfamide
indomethacin	influenza virus vaccine	itraconazole	ketoprofen	ketorolac
lansoprazole	leflunomide	lepirudin	levamisole	levofloxacin
levothyroxine	liothyronine	lovastatin	medroxyprogesterone	mefenamic acid
megestrol	memantine	metandienone	methimazole*	methyl dopa
Methyl prednisolone	methylphenidate	Methylsalicylate ointment	metronidazole	miconazole (intravaginal,

		(topical)		oral, systemic*)
morizine hydrochloride*	moxifloxacin	nalidixic acid	naproxen	neomycin
norfloxacin	noscapine	ofloxacin	olsalazine	omeprazole
orlistat	oxandrolone	oxaprozin	Oxolamine	oxymetholone
paclitaxel	pantoprazole	paroxetine	penicillin G, intravenous	pentoxifylline
phenylbutazone	phenytoin*	piperacillin	piroxicam	prasugrel
pravastatin	prednisone*	propafenone	propoxyphene	propranolol
propylthiouracil*	quinidine	quinine	rabeprazole	ranitidine*
rofecoxib	roxithromycin	sertraline	simvastatin	stanozolol
streptokinase	sulfamethizole	sulfamethoxazole	sulfinpyrazone	sulfisoxazole
sulindac	tamoxifen	tegafur	telithromycin	tetracycline
thyroid	ticarcillin	Tienilic acid	ticlopidine	tissue plasminogen activator (t-PA)
tolbutamide	tolterodine	toremifene	tramadol	trimethoprim /sulfamethoxazole
urokinase	valproate	vitamin E	voriconazole	zafirlukast
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.				

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

Table 6. ENDOGENOUS FACTORS

edema	hyperlipemia
hereditary coumarin resistance	hypothyroidism
	nephrotic syndrome

Table 7. EXOGENOUS FACTORS

Potential drug interactions with TARO-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
Enzyme inhibitors	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*

Table 8. Specific Drugs Reported

alcohol*	aminoglutethimide	amobarbital
aprepitant	atorvastatin	azathioprine
bosentan	butabarbital	butalbital
carbamazepine	chloral hydrate*	chlordiazepoxide
chlorthalidone	cholestyramine*	corticotropin
cortisone	Warfarin sodium underdose	cyclophosphamide*
dicloxacillin	ethchlorvynol	fosaprepitant
glutethimide	griseofulvin	haloperidol
meprobamate	6-mercaptopurine	methimazole*

moricizine hydrochloride*	nafcillin	paraldehyde
pentobarbital	phenobarbital	phenytoin*
prednisone*	primidone	propylthiouracil*
rалoxifene	rifampin	rifapentine
ranitidine*	secobarbital	spironolactone
sucralfate	trazodone	vitamin C (high dose)
vitamin K		
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 TARO-WARFARIN Tablets. Few, adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between natural medicines and warfarin sodium. 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 the Warfarin Sodium tablets 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 Sodium tablets. However, the effects of ginseng can be variable (increased or decreased effect of Warfarin Sodium tablets) and the combination should be avoided or more careful monitoring is warranted.
- Coenzyme Q₁₀ (ubidecarenone) and St. John's wort are associated most often with a DECREASE in the effects of Warfarin Sodium tablets.

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 Sodium tablets. Conversely, other natural medicines may have coagulant properties when taken alone or may decrease the effects of Warfarin Sodium tablets. Some botanicals and foods (green vegetables such as broccoli) can interact with TARO-WARFARIN through CYP450 interactions (eg, echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort).

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. The most widely recognized common natural medicines names are listed.

Table 9. Natural medicines that contain coumarins with potential anticoagulant effects:

Agrimony ^a (<i>Argimonia eupatoria</i>)	Licorice ^d (<i>Glycyrrhiza globra</i>)
Alfalfa (<i>Medicago sativa</i>)	Meadowsweet ^b (<i>Spiræa ulmaria</i>)
Aniseed (<i>Pimpinella anisum</i>)	Nettle (<i>Urtica dioica</i>)
Arnica	Parsley (<i>Carum petroselinum</i>)
Asa Foetida (<i>Asafetida</i>)	Passion Flower (<i>Passiflora edulis</i>)
Bogbean ^b (<i>Menyanthis folium</i>)	Prickley Ash - Northern (<i>Zanthoxylum americanum</i>)
<i>Peumus Boldo</i>	Quassia (<i>Amara</i>)
Buchu (<i>Barosmae boldo</i>)	Red Clover (<i>Trifolium pratense</i>)
Paprika (<i>Capsicum</i>)	Sweet Clover (<i>Melilotus officinalis</i>)
Cassia ^c	Sweet Woodruff (<i>Galii odorati herba</i>)
Celery (<i>Apium graveolens</i>)	Tonka Beans (<i>Dipteryx odorata</i>)
Chamomile - German and Roman (<i>Anthemis nobilis</i>)	Wild Carrot (<i>Daucus carota</i>) Wild Lettuce (<i>Lactuca virosa</i>)
Dandelion ^c (<i>Taraxacum officinale</i>)	Dong Quai (<i>Angelica sinensis</i>)
Fenugreek (<i>Trigonella fœnumgræcum</i>)	Horse Chestnut (<i>Æsculus hippocastanum</i>)
Horseradish (<i>Cochleria armoracia</i>)	

Miscellaneous natural medicines with anticoagulant properties:

Bladder Wrack (*Fucus vesiculosus*) Pau d'arco (*Tabebuia avellanedæ*)

Table 10. Natural medicines that contain salicylate and/or have antiplatelet properties:

Agrimony ^a	Ginger
Aloe Gel	Ginko Biloba
Aspen (<i>Populus tremuloides</i>)	Ginseng (<i>Panax spp</i>) ^e
Black Cohosh (<i>Cimicifuga racemosa</i>)	Licorice ^c
Black Haw (<i>Viburnum prunifolium</i>)	Meadowsweet ^b
Bogbean ^b	Onion ^e (<i>Allium cepa</i>)
Cassia ^d	Policosanol
Clove (<i>Eugenia caryophyllus</i>)	Poplar (<i>Populi gemma</i>)
Cranberry	Senega (<i>Polygala</i>)
Dandelion ^d	Tamarind (<i>Tamarindus Indica</i>)
Feverfew (<i>Chrysanthemum parthenum</i>)	Willow (<i>Salix nigra</i>)
Garlic ^e (<i>Tremuloides</i>)	Wintergreen (<i>Gaultheria procumbens</i>)
German Sarsaparilla (<i>Corex arenaria</i>)	

Table 11. Natural medicines with fibrinolytic properties:

Bromelains (<i>Bromelainum</i>)	Ginseng (<i>Panax spp</i>) ^e
Capsicum ^c	Inositol Nicotinate
Garlic ^e	Onion ^e

Table 12. Natural medicines with coagulant properties:

Green vegetables	Goldenseal (<i>Chrysanthemum</i>)
Mistletoe (<i>Viscum album</i>)	St John's wort (<i>hypericum perforatum</i>)
Yarrow (<i>Achillea millefolium</i>)	

-
- a. Contains coumarins, has antiplatelet properties, and may have coagulant properties due to possible vitamin K content.
 - b. Contains coumarins and salicyclate.
 - c. Contains coumarins and has fibrinolytic properties.
 - d. Contains coumarins and has antiplatelet properties.
 - e. Has antiplatelet and fibrinolytic properties.

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 \geq 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 sodium (resulting in a higher INR).

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

Caution should be observed when warfarin sodium (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.

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). Warfarin is contraindicated in any unsupervised patients with conditions associated with potential high level of noncompliance such as senility, alcoholism, or psychosis or other lack of patient cooperation.. 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 are recommended in the elderly (see **DOSAGE** and **ADMINISTRATION**).

Use in Pregnancy

TARO-WARFARIN exposure during pregnancy can cause pregnancy loss, birth defects, or fetal death. Discuss pregnancy planning with females of reproductive potential who are on TARO-WARFARIN therapy (see **CONTRAINDICATIONS**, Pregnancy).

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 sodium tablets in pediatric patients has been documented for the prevention and treatment of thromboembolic events.

Adequate and well-controlled studies with Warfarin Tablets have not been conducted in any pediatric population, and the optimum dosing, safety, and efficacy in pediatric patients is unknown. Pediatric use of Warfarin Tablets is based on adult data and recommendations, and available limited pediatric data from observational studies and patient registries. Pediatric patients administered Warfarin Tablets should avoid any activity or sport that may result in traumatic injury.

The developing hemostatic system in infants and children results in a changing physiology of thrombosis and response to anticoagulants. Dosing of warfarin in the pediatric population varies by patient age, with infants generally having the highest, and adolescents having the lowest milligram per kilogram dose requirements to maintain target INRs. Because of changing warfarin requirements due to age, concomitant medications, diet, and existing medical condition, target INR ranges may be difficult to achieve and maintain in pediatric patients, and more frequent INR determinations are recommended. Bleeding rates varied by patient population and clinical care center in pediatric observational studies and patient registries.

Infants and children receiving vitamin K–supplemented nutrition, including infant formulas, may be resistant to warfarin therapy, while human-milk–fed infants may be sensitive to warfarin therapy.

ADVERSE REACTIONS

Potential adverse reactions to TARO-WARFARIN (warfarin sodium) tablets may include:

Hemorrhage

Hemorrhage, ranging from minor to severe bleeding (including fatal outcomes), can occur during therapy with TARO-WARFARIN. Hemorrhage may occur in any tissue or organ, manifesting as external or internal bleeding with associated symptoms and complications. This is a consequence of the anticoagulant effect.

Typically, the following body systems may be affected:

- upper (gingival bleeding, hematemesis) or lower (melena, hematochezia, rectal bleeding) gastrointestinal tract
- Retroperitoneal hemorrhage can also occur.
- respiratory tract (epistaxis, hemoptysis), including rare cases of pulmonary alveolar hemorrhage

- genitourinary tract (hematuria, vaginal bleeding, menorrhagia)
- skin (contusion, ecchymosis, and petechia)

Central nervous system hemorrhage, including intracranial hemorrhage or spinal hematoma, ocular, intra-articular, pleural, pericardial, adrenal, and hepatic hemorrhage may also occur.

Some hemorrhagic complications may present as signs and symptoms that are not immediately identified as resulting from hemorrhage.

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, anaemia, purple toe syndrome, fatigue, lethargy, malaise, pallor, syncope or unexplained shock. Therefore, the possibility of haemorrhage should be considered in evaluating the condition of any anticoagulated patients 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).

Systemic atheroemboli and cholesterol microemboli (see WARNINGS)

Post-marketing Adverse reactions

The following adverse reactions have been reported from postmarketing experience with warfarin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and lymphatic system disorders: anemia

Cardiac disorders: angina, chest pain, pericardial haemorrhage

Endocrine disorders: adrenal haemorrhage

Eye disorders: eye haemorrhage

Gastrointestinal disorders: abdominal pain including cramping, abdominal distention, diarrhea, dysgeusia, dysphagia, flatulence/bloating, gingival bleeding, haematemesis, haematochezia, maelena, nausea, rectal haemorrhage, retroperitoneal haemorrhage, taste perversion, vomiting

General disorders and administration site conditions: asthenia, fatigue, edema, swelling feeling

cold and chills, malaise, pain pallor, fever

Hepatobiliary disorders: hepatitis, hepatic haemorrhage, jaundice, cholestatic hepatic injury

Immune system disorders: anaphylactic reaction: hypersensitivity/allergic reactions

Investigations: hepatic enzyme increased

Musculoskeletal, connective tissue and bone disorders: arthralgia, haemarthrosis, myalgia

Nervous system disorders: dizziness, headache, haemorrhage intracranial, paraesthesia, paralysis, spinal haematoma, cold intolerance, coma, loss of consciousness,

Psychiatric disorders: lethargy

Renal and urinary disorders: haematuria, acute kidney injury

Reproductive system and breast disorders: vaginal haemorrhage, menorrhagia

Respiratory, thoracic and mediastinal disorders: epistaxis, dyspnoea, haemoptysis, haemothorax, pulmonary alveolar haemorrhage, pulmonary calcification

Skin and subcutaneous tissue disorders: ecchymosis, pruritus, rash,

alopecia, dermatitis, petechia, urticaria, skin necrosis, dermatitis bullous calciphylaxis

Vascular disorders: haemorrhage, hypotension, syncope, vasculitis, shock, blue toe syndrome, embolism arterial, fat embolism, necrosis, systemic cholesterol microembolization,

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.

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) unexplained fall in hemoglobin) is a manifestation of excessive anticoagulation.

Treatment

The treatment of excessive anticoagulation is based on the level of the INR, the presence or absence of bleeding, and clinical circumstances. Excessive anticoagulation, may be controlled by

discontinuing TARO-WARFARIN (warfarin sodium) tablet therapy and if necessary, by administration of oral or parenteral vitamin K₁. (Please see recommendations accompanying vitamin K₁ preparations prior to use.)

Such use of vitamin K₁ reduces responses to subsequent TARO-WARFARIN Tablets therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged INR. Resumption of warfarin administration reverses the effect of vitamin K₁, and a therapeutic 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 K₁. Prothrombin complex concentrate (PCC), fresh frozen plasma, or activated Factor VII treatment may be considered if the requirement to reverse the effects of Taro-Warfarin Tablets is urgent

A risk of hepatitis and other viral diseases is associated with the use of these blood products; PCC and activated Factor VII are also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to TARO-WARFARIN Tablet overdose.

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 TARO-WARFARIN Tablet 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 administration and dosage of TARO-WARFARIN (warfarin sodium) tablets must be individualized according to the patient's 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 TARO-WARFARIN Tablets.

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 aspirin 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 aspirin alone. In patients with acute coronary syndrome that were revascularised by percutaneous coronary intervention (PCI), clopidogrel is usually 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 aspirin (100 mg/day) for 3 months following myocardial infarction should be considered.

Renal Impairment

While no dosage adjustment is necessary for patients with renal failure, frequent monitoring of anticoagulation is advised in patients with compromised renal function to maintain warfarin dosage within the therapeutic range (see WARNINGS: Use in Patients with altered glomerular integrity).

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.

Initial Dosage

The dosing of TARO-WARFARIN Tablets must be individualized according to the 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. It is recommended that TARO-WARFARIN Tablets 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 TARO-WARFARIN Tablets. Elderly and Asian patients may require lower initiation and maintenance doses of TARO-WARFARIN Tablets (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 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 TARO-WARFARIN Tablets persists beyond 24 hours. If the patient forgets to take the prescribed dose of TARO-WARFARIN Tablets 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.

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 TARO-WARFARIN Tablets 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 TARO-WARFARIN Tablet therapy. When discontinuing TARO-WARFARIN Tablets even for a short period of time, the benefits and risks should be strongly considered.

Conversion from Heparin Therapy

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

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

As heparin may affect the PT, patients receiving both heparin and TARO-WARFARIN Tablets 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.

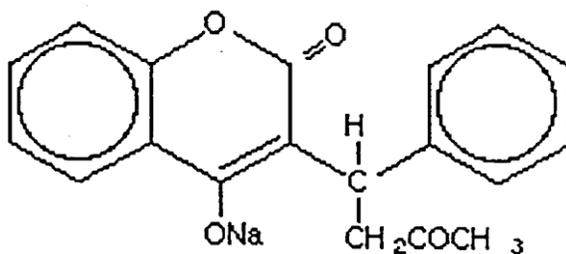
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Warfarin sodium, U.S.P.

Chemical Name: 3-(a-acetyl-benzyl)-4-hydroxycoumarin sodium salt isopropyl clathrate

Structural Formula:



. 1/2C₃H₈O

Molecular Formula: C₁₉H₁₅NaO₄ . 1/2C₃H₈O

Molecular Weight: 330.31 + 30.05

Description:

Warfarin sodium, U.S.P., a Vitamin K dependent factor anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. Warfarin is a coumarin derivative and is available as a racemic mixture of the 2 optical isomers of the sodium salt. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. 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. The pH is between 7.2 and 8.3, in a solution (1 in 100). The melting point of the free acid is between 157° - 167° C, range not to exceed 4°C. The pKa is 5.05.

Composition:

TARO-WARFARIN (warfarin sodium) tablets, U.S.P., contain the following ingredients: magnesium stearate, lactose anhydrous, pregelatinized corn starch and colour dye which varies in each tablet strength.

1 mg: D&C Red #6 - Lake
2 mg: FD&C Blue #2 - Lake and FD&C Red #40 - Lake
2.5 mg: FD&C Blue #2 - Lake and D&C Yellow #10 - Lake

3 mg: FD&C Red #40 - Lake, D&C Yellow #10 - Lake and FD&C Blue #2 - Lake
 4 mg: FD&C Blue # 1- Lake
 5 mg: D&C Yellow #10 - Lake and D&C Red #6 - Lake
 6 mg: D&C Yellow #10 - Lake and FD&C Blue #2 - Lake
 7.5 mg: D&C Yellow #10 - Lake
 10 mg: Dye free

Stability and Storage Recommendations:

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

Special Handling Instructions

Pharmacy and clinical personnel who are pregnant should avoid exposure to crushed or broken tablets (see **WARNINGS, Pregnancy**).

AVAILABILITY OF DOSAGE FORMS

TARO-WARFARIN (warfarin sodium) tablets, USP are single-scored and engraved as follows:

Strength	Imprint Side 1	Imprint Side 2	Color
1.0 mg	WARFARIN 1	TARO	Pink
2.0 mg	WARFARIN 2	TARO	Lavender
2.5 mg	WARFARIN 2½	TARO	Green
3.0 mg	WARFARIN 3	TARO	Tan
4.0 mg	WARFARIN 4	TARO	Blue
5.0 mg	WARFARIN 5	TARO	Peach
6.0 mg	WARFARIN 6	TARO	Teal
7.5 mg	WARFARIN 7½	TARO	Yellow
10.0 mg	WARFARIN 10	TARO	White

Supplied in bottles and blister packs of 100 for the 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg strengths.

Supplied in bottles of 250 for the 1, 2, 2.5, 4 and 5 mg strengths.

Supplied in bottles of 1000 for the 1, 2, 2.5, 3, 4, 5 and 6 mg strengths.

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).

BIBLIOGRAPHY

1. Peterson P, *et al*, Placebo Controlled, Randomized Trial Of Warfarin And Aspirin For Prevention Of Thromboembolic Complications In Chronic Atrial Fibrillation: The Copenhagen AFASAK Study. *Lancet*. 1989;1:175-9.
2. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study final results. *Circulation*. 1991;84:527-539.
3. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323: 1505- 1511.
4. Connolly SJ, *et al*, Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *JACC*. 1991;18:349-355.
5. Ezekowitz MD, *et al*, Warfarin in the Prevention of Stroke Associated with Nonrheumatic Atrial Fibrillation. *N Engl J Med*. 1992;327:1406-1412.
6. Laupacis A., M.D. *et al*, Antithrombotic Therapy in Atrial Fibrillation. *Chest*; 102.4 Oct. 1992 suppl. p. 4265-4335.
7. Smith P., *et al*.: The Effect of Warfarin on Mortality and Reinfarction After Myocardial Infarction (WARIS). *N. Engl J Med*. 1990;323:147-152.
8. Hirsh J., et al: Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutical Range. *Chest*1995;108(4):231s-246s.
9. Stroke Prevention in Atrial Fibrillation Investigators: Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*, 1996;348(9028):633-638.
10. Hylek EM., et al: An analysis of the Lowest Effective Intensity of Prophylactic Anticoagulation for Patients with Nonrheumatic Atrial Fibrillation., *N Eng J Med*, 1996;335:540-546.

11. Warkentin TE, et al. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997; 127: 804-812.
12. Spiers ASD, Mibashan RS. Increased warfarin requirement during mercaptopurine therapy: a new drug interaction. *Lancet* 1974; 2: 221-222.
13. Yamashita S, Paton T. The effects of warfarin and heparin on anticoagulation tests. *Can J Hosp Pharm* 1989; 42(1): 10-15.
14. Park EJ, Oh H, Kang TH, et al. An isocoumarin with hepatoprotective activity in Hep GE and primary hepatocytes from *Agrimonia pilosa*. *Arch Pharm Res* 2004;27(9):944-446.
15. Wang JP, Hsu MF, Teng CM. Antihemostatic effect of Hsien-Ho-T'sao (*Agrimonia pilosa*). *Am J Chin Med*. 1984 Summer;12(1-4):116-123.
16. Liu HC. Agrimony. In: *Chinese Natural Cures*. Black Dog & Leventhal. January 2006, pp 152
17. Coumadin® Product Monograph, Bristol-Myers Squibb Canada, submission control #217553, Date of Revision: September 4, 2018.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**TARO-WARFARIN
Warfarin Sodium Tablets**

Read this carefully before you start taking TARO-WARFARIN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TARO-WARFARIN.

Serious Warnings and Precautions

Risk of bleeding:

The most common side effect of TARO-WARFARIN is bleeding. The bleeding may be serious and life-threatening. You may be more at risk for bleeding if you have:

- a history of bleeding in your stomach or intestines (ulcers)
- high blood pressure
- heart disease
- problems with the blood circulation in your brain
- anemia
- cancer
- kidney disease
- experienced trauma or injury to your body.

Talk to your healthcare professional if you have any of the above conditions. You may also have a higher risk of bleeding if you take TARO-WARFARIN for a long time or if you take TARO-WARFARIN with certain other drugs. An INR level of 4.0 or greater is also a risk for bleeding. INR is a blood test that tells the level of blood clotting you have. Your healthcare professional will work to keep your INR within a range that is right for you. This will help lower the risk of bleeding. Notify your healthcare professional right away of any unusual bleeding or if signs or symptoms of bleeding occur (see “**What are possible side effects from using TARO-WARFARIN?**”).

What is TARO-WARFARIN used for?

- TARO-WARFARIN is an anticoagulant drug. “Anti” means against, and “coagulant” refers to blood clotting. An anticoagulant helps reduce clots from forming in the blood.
- TARO-WARFARIN is a narrow therapeutic index drug, which means that there is a narrow window 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

How does TARO-WARFARIN work?

TARO-WARFARIN partially blocks the re-use of vitamin K in your liver. Vitamin K is needed to make clotting factors. The clotting factors help the blood to clot and prevent bleeding. Vitamin K is found naturally in foods such as leafy, green vegetables and certain vegetable oils.

- TARO-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 TARO-WARFARIN last 2 to 5 days, but it is important for you to take your dose every day.

What are the ingredients in Taro-Warfarin?

Medicinal ingredient: warfarin sodium

Non-medicinal ingredients: magnesium stearate, lactose anhydrous, pregelatinized corn starch and colour dye which varies in each tablet strength:

1 mg:	Pink color - D&C Red #6 - Lake
2 mg:	Lavender - FD&C Blue #2 - Lake and FD&C Red #40 - Lake
2.5 mg:	Green - FD&C Blue #2 - Lake and D&C Yellow #10 - Lake
3 mg:	Tan - FD&C Red #40 - Lake, D&C Yellow #10 - Lake and FD&C Blue #2 - Lake
4 mg:	Blue - FD&C Blue # 1- Lake
5 mg:	Peach - D&C Yellow #10 - Lake and D&C Red #6 - Lake
6 mg:	Teal - D&C Yellow #10 - Lake and FD&C Blue #2 - Lake
7.5 mg:	Yellow - D&C Yellow #10 - Lake
10 mg:	White - Dye free

TARO-WARFARIN comes in the following dosage forms:

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

Each round, single-scored tablet is imprinted on one side with the word “WARFARIN” and the numeric strength of the tablet. The other side of the tablet is imprinted with the name “TARO”.

Be sure to check that the tablet shows “WARFARIN” and the right numeric strength before you take it.

Do not use TARO-WARFARIN if:

- you are pregnant, in particular if you have a high risk pregnancy. Use effective measures to avoid pregnancy while taking TARO-WARFARIN. This is very important because your unborn baby could be seriously harmed if you take TARO-WARFARIN while you are pregnant. Your baby could be born with birth defects or could die.
- you have recently had or are planning to have surgery of the eyes, central nervous system, or any major surgery.

- you have certain conditions such as:
 - stomach or intestinal bleeding or ulcers
 - bleeding in the lungs or kidneys, bladder or urethra
 - cerebral hemorrhage (bleeding in the brain)
 - heart infection
 - swelling of the heart membrane or fluid in the heart
 - a brain aneurysm (swelling of an artery that supplies blood to the brain).
- you have any medical procedure that can increase the risk of bleeding, such as spinal puncture or spinal anesthesia.
- you have severe uncontrolled high blood pressure.
- you are allergic to warfarin or any of the other ingredients in TARO-WARFARIN (see **What are the ingredients in TARO-WARFARIN?**).
- you consume alcohol.
- you practice any activity or sport that may result in serious injury.
- have psychosis (a mental disorder).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-WARFARIN. Talk about any health conditions or problems you may have, including if you:

- fall often
- have liver or kidney problems or a heart problem called congestive heart failure
- have high blood pressure
- have diabetes
- have a low blood count
- have cancer
- have a history of stroke or “mini-stroke” (transient ischemic attack)
- drink alcohol or have problems with alcohol abuse. Alcohol can affect your TARO-WARFARIN dose and should be avoided
- plan to have any surgery or a dental procedure. Tell all of your healthcare professionals and dentists that you are taking TARO-WARFARIN. They should talk to the healthcare professional who prescribed TARO-WARFARIN for you. This should be done before you have any surgery or dental procedure. Your TARO-WARFARIN may need to be stopped for a short time or you may need your dose adjusted
- are pregnant or planning to become pregnant Do not take TARO-WARFARIN during pregnancy.

Use effective measures to avoid pregnancy while taking TARO-WARFARIN. This is very important because your unborn baby could be seriously harmed if you take TARO-WARFARIN while you are pregnant. Your baby could be born with birth defects or could die.

- are breastfeeding. TARO-WARFARIN may cause your baby to bleed. Talk to your healthcare professional about the best way to feed your baby. If you choose to breastfeed while taking TARO-WARFARIN, both you and your baby should be carefully monitored

for bleeding problems

Other warnings you should know about:

- Death of skin tissue (skin necrosis or gangrene). This can happen soon after starting TARO-WARFARIN. It happens because blood clots form and block blood flow to an area of your body. You may need medical care right away to prevent death or loss (amputation) of your affected body part.
- TARO-WARFARIN may cause calcium build up in small blood vessels of the fat and skin tissues (calciophylaxis). This can cause hardening of your blood vessels.
- TARO-WARFARIN may cause pain in your toes. Your toes may look purple or dark in color. (“**Purple toes syndrome**”). This is due to the blood thinning effect of TARO-WARFARIN, which can cause the release of plaques that can block an artery. You may also experience other symptoms such as rash, gangrene (lack of blood supply to a body part), intense pain in the leg, foot, toes, back or in your side. You may need medical care right away to prevent death or loss (amputation) of your affected body part.
- TARO-WARFARIN should not be used if you have low platelet levels (**thrombocytopenia**) as this can be serious or life-threatening.
- **Blood Testing:**
 - To decide on the dosage of TARO-WARFARIN you need, your healthcare professional will regularly take a small amount of your blood. This will help to find out how fast your blood clots. This is often recorded as an INR (International Normalized Ratio). INR tests are very important. They help your healthcare professional determine what dosage of TARO-WARFARIN is right for you.
 - When you start taking TARO-WARFARIN, you may have INR tests every day for a few days, then periodically on a regular basis. Your healthcare professional will determine how often you need to have these tests done. **These INR tests and regular visits to a healthcare provider are very important for the success of TARO-WARFARIN therapy.** You will need to have these tests on a regular basis while you take TARO-WARFARIN. This will help keep your INR in the best range for your medical condition. Discuss with your healthcare professional the range that is right for you.
- Certain illnesses can affect your TARO-WARFARIN therapy. Call your health professional if you:
 - are throwing up
 - have loose or runny stools
 - have an infection
 - have a fever.
- Carry identification stating that you are taking TARO-WARFARIN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Some of your other medicines may affect the way TARO-WARFARIN works. Certain medicines may increase your risk of bleeding.

The following prescription medicines may interact with TARO-WARFARIN:

- Medicines to treat pain and inflammation called Non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen, celecoxib, diclofenac and naproxen.
- Blood thinners such as aspirin, clopidogrel, apixaban, rivaroxaban, dabigatran, ticagrelor, prasugrel and dipyridamole.
- Antidepressants in the class called selective serotonin reuptake inhibitors (SSRI) such as sertraline, paroxetine, fluoxetine, escitalopram and citalopram.
- Medicines to treat bacterial or antifungal infections such as amoxicillin, penicillin, azithromycin, ciprofloxacin, erythromycin, doxycycline, fluconazole, voriconazole and itraconazole.
- Other medicines that contain warfarin. Warfarin is the active ingredient in TARO-WARFARIN

Natural health products that may interact with TARO-WARFARIN include:

- bromelains
- coenzyme Q10
- danshen (*Colocasia antiquorum*)
- dong quai (*Angelica sinensis*)
- garlic
- ginkgo biloba
- ginseng
- St. John's wort

How TARO-WARFARIN may interact with food:

- Eat a normal balanced diet. Avoid big changes in your diet. Talk to your healthcare professional **before** you go on a diet.
- Eat a consistent amount of green, leafy vegetables. Do not make big changes in your diet. These vegetables have high amounts of Vitamin K. The amount of vitamin K in your daily diet may affect therapy with TARO-WARFARIN.
- Tell your healthcare professional if cranberry juice or other cranberry products are part of your normal diet.

How to take TARO-WARFARIN:

- Be sure to check that the tablet has “TARO-WARFARIN” written on one side and the

- correct numeric strength before you take it.
- **Take TARO-WARFARIN exactly the way your healthcare professional tells you and take it at the same time every day.**
 - You can take TARO-WARFARIN either with food or on an empty stomach.
 - Your dosage may change from time to time depending on your response to TARO-WARFARIN.
 - Do not start, stop, or change any medicine except on advice of your healthcare professional.
 - The dose of TARO-WARFARIN may be different for each patient. For example, older patients (age 60 years of age or older) seem to respond more to TARO-WARFARIN. As your age increases, you may need a lower dose of TARO-WARFARIN. Your healthcare professional will monitor your INR levels and will decide what dose is best for you. This dose may change from time to time.

Overdose:

If you think you have taken too much TARO-WARFARIN, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of TARO-WARFARIN, notify your healthcare professional right away.
- Take the dose as soon as possible on the same day,
- Do not take a double dose of TARO-WARFARIN the next day to make up for a missed dose.

What are possible side effects from using TARO-WARFARIN?

These are not all the possible side effects you may feel when taking TARO-WARFARIN. If you experience any side effects not listed here, contact your healthcare professional.

TARO-WARFARIN affects blood clotting, so most side effects are related to bleeding. TARO-WARFARIN can cause bleeding that can be serious and sometimes lead to death.

Your healthcare professional will work to keep your INR within a range that is right for you. This will help lower the risk of bleeding.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
• Bleeding from your nose		X	
• Bleeding of gums when brushing your teeth		X	
• Coughing up blood.		X	
• Unusual bruising (black-and-blue marks on your skin) for unknown reasons.		X	
• Headache, dizziness, or weakness fatigue, feeling tired, general feeling of illness (malaise) - (Anemia).		X	
• Bleeding from shaving or other cuts that do not stop.		X	
• Unusual pain or swelling.		X	
• Pink or dark brown urine.		X	
UNCOMMON			
• Allergic reactions: rash, itching, hives, trouble breathing, throat tightening or constriction, swelling of the face, lips or tongue, sudden low blood pressure.			X
• Unexpected bleeding from the vagina.		X	
• Bleeding in the brain: blurred vision, slurred speech, loss of movement, numbness, dizziness, headache, fits, loss of consciousness.			X
• Vomiting blood or your vomit looks like coffee grounds.		X	
• Blood in your stool: Red or black stools that may look like tar.		X	
RARE			
Any sores, changes in skin color or temperature, or severe pain on your skin. Skin necrosis (death of skin tissue).		X	
VERY RARE			
Purplish skin discoloration, pain in the foot and leg, tingling sensation in the foot. (Purple toe syndrome).		X	

More bleeding than usual when you get your menstrual period.		X	
UNKNOWN			
<ul style="list-style-type: none"> Changes in skin color or temperature, or severe pain on your skin. Calcium accumulation in small blood vessels of the fat and skin tissues (calciphylaxis). 		X	

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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting \(https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html\)](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the tablets at room temperature (15°C to 30°C).
- Protect from light.
- Keep out of reach and sight of children.

If you want more information about TARO-WARFARIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website \(https://health-products.canada.ca/dpd-bdpp/index-eng.jsp\)](https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) the manufacturer's website at <http://www.taro.ca>, or by calling 1-800-268-1975.

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