Product Monograph

Pr TARO-WARFARIN

Warfarin Sodium Tablets, USP

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

ANTICOAGULANT

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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 K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

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

Pharmacokinetics

Warfarin sodium is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. It is important that all warfarin sodium products provide the same ratio of enantiomers as that which is present in 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	

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

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

Pharmacogenomics

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

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

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

Elimination

The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-

warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

In the Elderly

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulation effects of warfarin. The cause of this increased sensitivity in this age group is not known. This increased 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. No dosage adjustment is necessary for patients with renal failure.

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)
AUC0-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%)
$AUC_{0\text{-}72h}$ (ng.hr/mL)	4716.72 4876.27 (24.33%)	4563.34 4667.06 (21.50%)	103.36 (96.29 - 110.96)
$AUC_{0\text{-}inf}$ (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%)
$AUC_{0\text{-}72h}$ (ng.hr/mL)	4691.52 4895.45 (29.03%)	4731.91 5012.25 (25.46%)	99.15 (95.70 - 102.72)
$AUC_{0\text{-}inf}$ (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, reinfarction and death.

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. cerebrovascular haemorrhage
3. aneurysms - cerebral, dissecting aorta
4. pericarditis and pericardial effusions
5. bacterial endocarditis

Threatened abortion, eclampsia and preeclampsia

Inadequate laboratory facilities

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

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

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin sodium or to any other components of TARO-WARFARIN Tablets.

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. 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)**

Haemorrhage

The most serious risks associated with anticoagulant therapy with TARO-WARFARIN (warfarin sodium) Tablets are haemorrhage in any tissue or organ (see WARNING BOX) and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of haemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Haemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected

tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

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.

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.

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". Discontinuation of TARO-WARFARIN Tablet therapy is recommended when such phenomena are observed. While the "purple toe syndrome" is reported to be reversible, other complications of microembolization may not be reversible.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain,

hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

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

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 judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

1. Severe to moderate hepatic or renal insufficiency.
2. Infectious diseases or disturbances of intestinal flora, such as sprue or as seen with antibiotic use.
3. Trauma which may result in internal bleeding.
4. Surgery or trauma resulting in large exposed raw surfaces.
5. Indwelling catheters.
6. Severe to moderate hypertension.
7. Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop

necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with warfarin 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. Diseases affecting the microvasculature or microcirculation, such as polycythemia vera, vasculitis, and severe diabetes.

Heparin-Induced Thrombocytopenia

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

Use in Nursing Mothers

Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times. The decision to breast-feed should be undertaken only after careful consideration of the available alternatives. Women who are breast-feeding and anticoagulated with warfarin should be very carefully monitored so that recommended INR values are not exceeded. It is prudent to perform coagulation tests on infants at risk for bleeding before advising women taking warfarin to breast-feed. Effects in premature infants have not been evaluated.

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. 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. Tables 1 and 2 provide a listing of factors, alone or in combination, which may effect the PT. However, other factors may also affect the anticoagulant response and the tables are provided for your reference only.

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 ratio/INR monitoring is therefore advisable.

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

Interactions

The complete *in vivo* inhibition of the CYP 2C9 isozyme, may be expected to result in lower maintenance dose requirement of warfarin. Individuals with allelic polymorphisms of CYP 2C9 have been identified and have been shown to have lower maintenance dose requirements of warfarin and increased risk of overanticoagulation. Acquired or inherited warfarin resistance should be suspected if large daily doses of 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.

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

Table 1

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

ENDOGENOUS FACTORS:

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

EXOGENOUS FACTORS:

Potential drug interactions with 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 ϕ Antibiotics ϕ Aminoglycosides (oral) Cephalosporins, parenteral Macrolides Penicillins, intravenous, high dose Quinolones (fluoroquinolones) Sulfonamides, long acting Tetracyclines Anticoagulants Anticonvulsants ϕ Antidepressants ϕ Anti-fungal Medications, Intravaginal, Systemic ϕ Antimalarial Agents	Antineoplastics ϕ Antiparasitic/ Antimicrobials Antiplatelet Drugs/ Effects Antithyroid Drugs ϕ Beta-Adrenergic Blockers Cholelitholytic Agents Diabetes Agents, Oral Diuretics ϕ Gastric Acidity and Peptic Ulcer Agents ϕ Gastrointestinal, Ulcerative Colitis Agents Gastrointestinal, Prokinetic Agents Gout Treatment Agents Hemorrheologic Agents Hepatotoxic Drugs Hyperglycemic Agents Hypertensive Emergency Agents Hypnotics ϕ Leukotriene Receptor Antagonists	Lipid Lowering Agents ϕ Bile Acid-Binding Resins ϕ Fibrates HMG-CoA Reductase Inhibitors ϕ 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 ϕ Steroids, Anabolic- (17-Alkyl Testosterone Derivatives) Thrombolytics Thyroid Drugs Tuberculosis Agents ϕ Uricosuric Agents Vaccines Vitamins ϕ

Specific Drugs Reported

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

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

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

Table 2

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

ENDOGENOUS FACTORS:		
edema hereditary coumarin (warfarin sodium) resistance	hyperlipemia hypothyroidism	nephrotic syndrome

EXOGENOUS FACTORS:

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

Classes of Drugs

Adrenal Cortical Steroid Inhibitors Antacids Antianxiety Agents Antiarrhythmics ϕ Antibiotics ϕ Anticonvulsants ϕ Antidepressants ϕ Anti-fungal Medications, Systemic ϕ Antihistamines Antineoplastics ϕ	Antipsychotic Medications Antithyroid Drugs ϕ Barbiturates Diuretics ϕ Enteral Nutritional Supplements Gastric Acidity and Peptic Ulcer Agents ϕ Hypnotics ϕ Immunosuppressives	Lipid Lowering Agents Bile Acid-Binding Resins ϕ HMG-CoA Reductase Inhibitors ϕ Natural Medicines Oral Contraceptives, Estrogen Containing Selective Estrogen Receptor Modulators Steroids, Adrenocortical ϕ Tuberculosis Agents ϕ Vitamins ϕ

Specific Drugs Reported

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

also: diet high in vitamin K, unreliable PT determinations

ϕ 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 Q_{10} (ubidecarenome) 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 natural medicines that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many natural medicines have several common names and scientific names.

Natural medicines that contain coumarins with potential anticoagulant effects:

Agrimony[c] (*Argimonia eupatoria*), Alfalfa (*Medicago sativa*), Aniseed (*Pimpinella anisum*), Arnica, Asa Foetida (*Asafetida*), Bogvean[a] (*Menyanthis folium*), Peumus Boldo, Buchu (*Barosmae boldo*), Paprika (*Capsicum*), Cassia[c], Celery (*Apium graveolens*), Chamomile - German and Roman (*Anthemis nobilis*), Dandelion[c] (*Taraxacum officinale*), Dong Quai (*Angelica*

sinesis), Fenugreek (*Trigonella foenumgraecum*), Horse Chestnut (*Aesculus hippocastanum*), Horseradish (*Cochleria armoracia*), Licorice[c] (*Glycrrhiza globra*), Meadowsweet[a] (*Spiraea ulmaria*), Nettle (*Urtica dioica),* Parsley (*Carum petroselinum),* Passion Flower (*Passiflora edulis),* Prickley Ash - Northern (*Zanthoxylum americanum),* Quassia (*Amara),* Red Clover (*Trifolium pratense),* Sweet Clover (*Melilotus officinalis),* Sweet Woodruff (*Galii odorati herba),* Tonka Beans (*Dipteryx odorata),* Wild Carrot (*Daucus carota),* Wild Lettuce (*Lactuca virosa).

Miscellaneous natural medicines with anticoagulant properties:

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

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

Agrimony[c], Aloe Gel, Aspen (*Populus tremuloides),* Black Cohosh (*Cimicifuga racemosa),* Black Haw (*Viburnum prunifolium),* Bogbean[a], Cassia[c], Clove (*Eugenia caryophyllus),* Dandelion[c], Feverfew (*Chrysanthenum parthenum),* Garlic[d] (*Tremuloides),* German Sarsaparilla (*Corex arenaria,* Ginger, Ginko Biloba, Ginseng (*Panax*)[d] Licorice[c], Meadowsweet[a], Onion[d] (*Allium cepa),* Policosanol, Poplar (*Populi gemma),* Senega (*Polygala),* Tamarind (*Tamarindus Indica),* Willow (*Salix nigra),* Wintergreen (*Gaultheria procumbens).

Natural medicines with fibrinolytic properties:

Bromelains (*Bromelainum),* Capsicum[b], Garlic[d], Ginseng (*Panax*)[d], Inositol Nicotinate, Onion[d]

Natural medicines with coagulant properties:

Goldenseal (*Chrysanthenum),* Mistletoe (*Viscum album),* Yarrow (*Achillea millefolium)*

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

Considerations for Increased Bleeding Risk

Warfarin is a narrow therapeutic range (index) drug, and additional caution should be observed when warfarin sodium is administered to certain patients. Reported risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥ 65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (**see PRECAUTIONS**) and long duration of warfarin therapy. Identification of risk factors for bleeding and certain genetic

variations in CYP2CP and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses (**see CLINICAL PHARMACOLOGY: Metabolism and DOSAGE AND ADMINISTRATION**). Bleeding is more likely to occur during the starting period and with a higher dose of warfarin sodium (resulting in a higher INR).

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

Caution should be observed when warfarin 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 patient with senility. Caution should be exercised with administration of warfarin sodium to elderly and/or debilitated patients in any situation or physical condition where added risk of hemorrhage is present. Low initiation and maintenance doses of warfarin are recommended in the elderly (see DOSAGE and ADMINISTRATION).

Use in Pregnancy

See CONTRAINDICATIONS

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. Difficulty achieving and

maintaining therapeutic PT ratio/INR ranges in the pediatric patient has been reported. More frequent PT ratio/INR determinations are recommended because of possible changing warfarin requirements.

ADVERSE REACTIONS

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

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

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

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

- Adverse reactions reported infrequently include:
  Body As A Whole: hypersensitivity/allergic reactions, pain, edema, asthenia, fever, headache, fatigue, lethargy, malaise, anemia, pallor
  Central and Peripheral Nervous System: dizziness, cold intolerance, coma, loss of consciousness, syncope and paresthesia, including feeling cold and chills
  Gastrointestinal: nausea, diarrhea, abdominal pain, including cramping, flatulence/bloating, vomiting
  Liver and Biliary: elevated liver enzymes, hepatitis, jaundice, cholestatic hepatic injury

Skin and Appendages: alopecia, rash, pruritus, urticaria, dermatitis, including bullous eruptions

Vascular, Extracardiac: angina syndrome, chest pain, systemic cholesterol microembolization, purple toes syndrome, vasculitis

Special Senses: taste perversion

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

Such use of vitamin K_1 reduces responses to subsequent TARO-WARFARIN Tablets therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT. Resumption of warfarin administration reverses the effect of vitamin K_1, and a therapeutic PT

can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

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

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

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X, which are also depressed along with the levels of Factor IX as a result of 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.

For management of a suspected drug overdose, contact your regional poison control centre.

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 ble eding. 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 withour 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 usally added. For high-risk patients with myocardial infarction (MI), including those with a large anterior MI, significant heart failure, intracardiac thrombus visible on echocardiography, or those with a history of a thromboembolic event, therapy with combined moderate-intensity warfarin (INR 2.0 to 3.0) plus low-dose aspirin (100 mg/day) for 3 months following myocardial infarction should be considered.

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). Use of a large loading dose may increase the incidence of haemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended.

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.

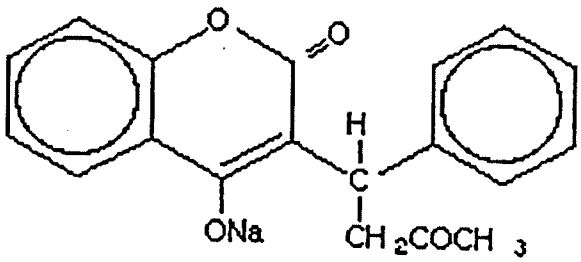
PHARMACEUTICAL INFORMATION

Drug Substance:

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

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

Structural Formula:



. $1/2C_3H_8O$

Molecular Formula: $C_{19}H_{15}NaO_4 . 1/2C_3H_8O$

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.

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.

INFORMATION TO THE PATIENT

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

1. What are TARO-WARFARIN Tablets?

- 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 margin between too much and too little of the drug. Too much drug may cause you to bleed more. Too little drug may let a harmful clot form.

2. How do TARO-WARFARIN Tablets work?

- TARO-WARFARIN Tablets partially block the re-use of vitamin K in your liver. Vitamin K is needed to make clotting factors that help the blood to clot and prevent bleeding. Vitamin K is found naturally in foods such as leafy, green vegetables and certain vegetable oils.
- TARO-WARFARIN Tablets begin 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 Tablets last 2 to 5 days, but it is important for you to take your dose everyday.

3. What should I tell my healthcare provider before starting TARO-WARFARIN Tablets

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

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

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. See "What should I avoid while taking TARO-WARFARIN Tablets?"

4. **What is the most important information I should know when taking TARO-WARFARIN Tablets?**

- Like all prescription drugs, TARO-WARFARIN Tablets may cause side effects. The most common side effect of TARO-WARFARIN Tablets is bleeding, which may be serious and life-threatening. However, the risk of serious bleeding is low when the effect of TARO-WARFARIN Tablets is within a range that is right for your specific medical condition. Notify your health care provider right away of any unusual bleeding or if signs or symptoms of bleeding occur (see "What are the possible side effects of TARO-WARFARIN Tablets).
- Do not take TARO-WARFARIN Tablets during pregnancy. Use effective measures to avoid pregnancy while taking TARO-WARFARIN Tablets.
- The dose of TARO-WARFARIN Tablets may be different for each patient. For example, older patients (age 60 years of age or older) appear to have a greater-than-expected response to TARO-WARFARIN Tablets so that as patient age increases, a lower dose of TARO-WARFARIN Tablets may be needed. Your health care provider will decide what dose is best for you. This dose may change from time to time.
- To decide on the dosage of TARO-WARFARIN Tablets you need, your health care provider will take a small amount of your blood to find out your prothrombin time, protime, or PT, for short. Protimes are often recorded as an INR (International Normalized Ratio), a standard way of reporting protimes.
- PT/INR tests are very important. They help your health care provider see how fast your blood is clotting and whether your dosage of TARO-WARFARIN Tablets should change.
- When you start taking TARO-WARFARIN Tablets, you may have PT/INR tests every day for a few days, then perhaps one time every week. **These PT/INR tests and regular visits to a health care provider are very important for the success of therapy with TARO-WARFARIN Tablets.** PT/INR tests will be needed at periodic intervals (such as one time per month) throughout your course of therapy to keep your PT/INR in the best range for your medical condition. Discuss with your health care provider the range that is right for you.
- Eat a normal balanced diet maintaining a consistent level of green leafy vegetables that contain high amounts of Vitamin K since the amount of vitamin K in your daily diet may affect TARO-WARFARIN Tablet therapy.
- Report any illness, such as throwing up (vomiting), loose or runny stools (diarrhea), an infection or fever to your health care provider.

- Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your healthcare provider may need to check you.
- Tell anyone giving you medical or dental care that you are taking TARO-WARFARIN Tablets.
- Tell your healthcare provider about any planned surgeries, medical or dental procedures. Your TARO-WARFARIN Tablets may have to be stopped for a short time or you may need your dose adjusted.
- Carry identification stating that you are taking TARO-WARFARIN Tablets.

5. How should I take TARO-WARFARIN Tablets?

- **Take TARO-WARFARIN Tablets exactly the way your health care provider tells you and take it at the same time every day.** You can take TARO-WARFARIN Tablets either with food or on an empty stomach. Your dosage may change from time to time depending on your response to TARO-WARFARIN Tablets.
- If you miss a dose of TARO-WARFARIN Tablets, notify your health care provider right away. Take the dose as soon as possible on the same day, but do not take a double dose of TARO-WARFARIN Tablets the next day to make up for a missed dose.

6. What are the possible side effects of TARO-WARFARIN Tablets?

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

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

- headache, dizziness, or weakness
- bleeding from shaving or other cuts that does not stop
- nosebleeds
- bleeding of gums when brushing your teeth
- coughing up blood
- vomiting blood or material that looks like coffee grounds
- unusual bruising (black-and-blue marks on your skin) for unknown reasons

- pink or dark brown urine
- red or black color in your stool
- more bleeding than usual when you get your menstrual period or unexpected bleeding from the vagina
- unusual pain or swelling

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

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

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

7. What should I avoid while taking TARO-WARFARIN Tablets?

- Do not start, stop, or change any medicine except on advice of your health care provider. TARO-WARFARIN Tablets interact with many different drugs, including aspirin and aspirin-containing ointments and skin creams as well as natural medicines (e.g., bromelains, coenzyme Q_{10}, danshen (*Colocasia antiquorum*), dong quai (*Angelica sinensia*), garlic, ginkgo biloba, ginseng and St. John's wort). Tell your health care provider about any prescription and non-prescription (over-the-counter) drugs that you are taking including occasional use of headache medications.
- Do not take any other medicines that contain warfarin. Warfarin is the active ingredient in TARO-WARFARIN Tablets.
- Do not make drastic changes in your diet, such as eating large amounts of green, leafy

vegetables. The amount of vitamin K in your daily diet may affect therapy with TARO-WARFARIN Tablets.

- Avoid intake of cranberry juice or any other cranberry products. Notify your healthcare provider if any of these products are part of your normal diet.
- Do not attempt to change your weight by dieting, without first checking with your health care provider.
- Avoid alcohol consumption.
- Do not participate in any activity or sport that may result in serious injury.
- Avoid cutting yourself.

8. What do TARO-WARFARIN Tablets look like?

TARO-WARFARIN Tablets are available in many strengths, and each strength has a unique tablet color:

Tablet Strength	Tablet Color
1.0 mg	Pink
2.0 mg	Lavender
2.5 mg	Green
3.0 mg	Tan
4.0 mg	Blue
5.0 mg	Peach
6.0 mg	Teal
7.5 mg	Yellow
10.0 mg	White

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.

TOXICOLOGY

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

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

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