CENTER FOR DRUG EVALUATION AND RESEARCH

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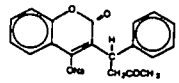
Warfarin Sodium Tablets, USP

Crystalline

Rx only

Anticoagulant

DESCRIPTION Warfarin Sodium, USP, is an anticoagulant which acts by inhibiting vitamin K- dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt and is a racemic mixture of the R and S enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its molecular formula is $C_{19}H_{15}NaO_4$ and its molecular weight is 330.32 and its structural formula may be represented by the following:



Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

Warfarin Sodium Tablets, USP for oral use also contain:

All strengths: Anhydrous lactose, corn starch and magnesium stearate

1 mg: D&C red #6 Barium Lake.
2 mg: FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake.
2.5 mg: FD&C blue #2 Aluminum Lake, D&C yellow #10 Aluminum Lake.
3 mg: FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake, D&C yellow #10 Aluminum Lake.
4 mg: FD&C blue #2 Aluminum Lake.
5 mg: D&C yellow #10 Aluminum Lake, D&C red #6 Barium Lake.
6 mg: D&C yellow #10 Aluminum Lake, FD&C blue #2 Aluminum Lake.
7.5 mg: D&C yellow #10 Aluminum Lake.
10 mg: Dye Free

CLINICAL PHARMACOLOGY Crystalline 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 activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of crystalline warfarin sodium 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: Crystalline 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.

Absorption: Crystalline warfarin sodium is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution: There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see WARNINGS - Lactation). Approximately 99% of the drug is bound to plasma proteins.

Metabolism: The elimination of warfarin is almost entirely by metabolism. Crystalline 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. The Cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion: The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Elderly: There are no significant age-related differences in the pharmacokinetics of racemic warfarin. Limited information suggests that there is no difference in the clearance of S-warfarin in elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly compared to the young. Older patients (60 years or older) appear to have an increased PT/INR responsiveness to the anticoagulant effects of warfarin. As patient age increases, less warfarin is required to produce a therapeutic level of anticoagulation. The cause of the increased responsiveness to warfarin is not known.

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

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

Clinical Trials

Atrial Fibrillation (AF): In five prospective randomized controlled clinical trials involving 3711 patients with nonrheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (See Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.8 to 2.7% (See Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.

TABLE 1

CLINICAL STUDIES OF WARFARIN IN NON RHEUMATIC AF PATIENTS*

Study	N		PT Ratio	INR	Thromboembolism		% Major Bleeding	
	Warfarin-Treated Patients	Control Patients			% Risk Reduction	p value	Warfarin-Treated Patients	Control Patients
AFASAK	335	336	1.5-2.0	2.8-4.2	60	0.027	0.6	0.0
SPAF	210	211	1.3-1.8	2.0-4.5	67	0.01	1.9	1.9
BAATAF	212	208	1.2-1.5	1.5-2.7	86	<0.05	0.9	0.5
CAFA	187	191	1.3-1.6	2.0-3.0	45	0.25	2.7	0.5
SPINAF	260	265	1.2-1.5	1.4-2.8	79	0.001	2.3	1.5

*All study results of warfarin vs. control are based on intention-to-treat analysis and include ischemic stroke and systemic thromboembolism, excluding hemorrhage and transient ischemic attacks.

Myocardial Infarction: WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. (But note that a lower INR was achieved and increased bleeding was associated with INR's above 4.0; see Dosage and Administration.) The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table:

TABLE 2

Event	Warfarin (N=607)	Placebo (N=607)	RR (95%CI)	% Risk Reduction (p-value)
Total Patient Years of Follow-up	2018	1944		
Total Mortality	94(4.7/100 py)	123(6.3/100 py)	0.76 (0.60, 0.97)	24 (p=0.030)
Vascular Death	82(4.1/100 py)	105(5.4/100 py)	0.78 (0.60,1.02)	22 (p=0.068)
Recurrent MI	82(4.1/100 py)	124(6.4/100 py)	0.66 (0.51, 0.85)	34 (p=0.001)
Cerebrovascular Event	20(1.0/100 py)	44(2.3/100 py)	0.46 (0.28, 0.75)	54 (p=0.002)

RR=Relative risk; Risk reduction=(1-RR); CI=Confidence Interval; MI=Myocardial Infarction; py=patient years

Mechanical and Bioprosthetic Heart Valves: In a prospective, randomized, open label, positive-controlled study (Mok et al, 1985) in 254 patients, the thromboembolic-free interval was found to be significantly greater in patients with mechanical prosthetic heart valves treated with warfarin alone compared with dipyridamole-aspirin ($p<0.005$) and pentoxifylline-aspirin ($p<0.05$) treated patients. Rates of thromboembolic events in these groups were 2.2, 8.6, and 7.9/100 patient years, respectively. Major bleeding rates were 2.5, 0.0, and 0.9/100 patient years, respectively.

In a prospective, open label, clinical trial (Saour et al, 1990) comparing moderate (INR 2.65) vs. high intensity (INR 9.0) warfarin therapies in 258 patients with mechanical prosthetic heart valves, thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events/100 patient years, respectively). Major bleeding was more common in the high intensity group (2.1 events/100 patient years) vs. 0.95 events/100 patient years in the moderate intensity group.

In a randomized trial (Turpie et al, 1988) in 210 patients comparing two intensities of warfarin therapy (INR 2.0-2.25 vs. INR 2.5-4.0) for a three month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (major hemorrhages 4.8%) vs. none in the lower intensity.

INDICATIONS AND USAGE Warfarin sodium tablets, USP are indicated for the prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism.

Warfarin sodium tablets, USP are indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

Warfarin sodium tablets, USP are indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

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

Pregnancy: Warfarin sodium tablets, USP is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus *in utero*. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following *in utero* exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and still birth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

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

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

Miscellaneous: major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS The most serious risks associated with anticoagulant therapy with sodium warfarin are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Warfarin, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT) ratio/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and warfarin are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

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E 2

acebo (=507)	RR (95%CI)	% Risk Reduction (p-value)
44		
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5(5 4/100 py)	0.78 (0.60,1.02)	22 (p=0.068)
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Caution should be observed when warfarin is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis and/or gangrene is present.

Anticoagulation therapy with warfarin may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of warfarin therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

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

Heparin-induced thrombocytopenia: Warfarin should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR ratio in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

Lactation: Warfarin appears in the milk of nursing mothers in an inactive form. Infants nursed by mothers treated with warfarin sodium had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.

Severe to moderate hepatic or renal insufficiency.

Infectious diseases or disturbances of intestinal flora: sprue, antibiotic therapy.

Trauma which may result in internal bleeding.

Surgery or trauma resulting in large exposed raw surfaces.

Indwelling catheters.

Severe to moderate hypertension.

Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concurrent anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with warfarin may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Miscellaneous: polycythemia vera, vasculitis, and severe diabetes.

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

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

Patients with congestive heart failure may exhibit greater than expected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

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

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

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with warfarin through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for INCREASED PT or INR response:

ENDOGENOUS FACTORS:

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

EXOGENOUS FACTORS:

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

Classes of Drugs:

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

Specific Drugs Reported

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

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

†Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

ENDOGENOUS FACTORS:

edema	hyperlipemia	nephrotic syndrome
hereditary coumarin resistance	hypothyroidism	

EXOGENOUS FACTORS:

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

Classes of Drugs

Adrenal Cortical Steroid Inhibitors	Anticonvulsants†	Barbiturates	Gastric Acidity and Peptic Ulcer Agents†	Estrogen Containing Steroids, Adrenocortical†
Antacids	Antidepressants†	Diuretics†	Hypnotics†	Tuberculosis Agents†
Antianxiety Agents	Antihistamines	Enteral Nutritional Supplements	Hypolipidemics†	Vitamins†
Antiarrhythmics†	Antineoplastics†	Fungal Medications, Systemic†	Immunosuppressives	
Antibiotics†	Antipsychotic Medications		Oral Contraceptives,	
	Antithyroid Drugs†			

Specific Drugs Reported

alcohol†	chlordiazepoxide	glutethimide	paraldehyde	rifampin
aminoglutethimide	chlortrianisene	griseofulvin	pentobarbital	secobarbital
amobarbital	cholestyramine†	haloperidol	phenobarbital	spironolactone
azathioprine	cortisone	meprobamate	phenytoin†	sucralfate
butabarbital	cortisone	6-mercaptopurine	prednisone†	trazodone
butalbital	cyclophosphamide†	methimazole†	primidone	vitamin C (high dose)
carbamazepine	dicloxacillin	mirtazapine hydrochloride†	propythiouracil†	vitamin K
chloral hydrate†	ethchlorvynol	nafcillin	ranitidine†	warfarin underdosage

also: diet high in vitamin K
unreliable PT/INR determinations

†Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of warfarin sodium tablets, USP on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

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

Effect on Other Drugs: Warfarin may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Special Risk Patients: Warfarin is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

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

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

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

Information for Patients: The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics) and other over-the-counter medications except on advice of the physician. Avoid excessive alcohol consumption. Do not take warfarin during pregnancy and do not become pregnant while taking it (see Contraindications). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that warfarin is being taken. If the prescribed dose of warfarin is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of warfarin the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with warfarin. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with warfarin is discontinued, patients should be cautioned that the anticoagulant effects of warfarin may persist for about 2 to 5 days. **Patients should be informed that all warfarin products represent the same medication, and should not be taken concomitantly, as overdosage may result.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and mutagenicity studies have not been performed with warfarin. The reproductive effects of warfarin have not been evaluated.

Use in Pregnancy: Pregnancy Category X - See CONTRAINDICATIONS.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established. In randomized, controlled clinical trials. However, the use of warfarin in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

ADVERSE REACTIONS Potential adverse reactions to warfarin may include:

- Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See OVERDOSAGE-Treatment.)
- Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.
- Necrosis of skin and other tissues. (See WARNINGS.)
- Adverse reactions reported infrequently include: hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritis, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

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

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

OVERDOSAGE

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

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

Such use of vitamin K_1 reduces response to subsequent warfarin therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of warfarin administration reverses the effect of vitamin K, and a therapeutic PT/INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

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

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

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of warfarin treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

DOSAGE AND ADMINISTRATION The dosage and administration of warfarin sodium tablets, USP must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See Laboratory Control below for full discussion on INR).

Venous Thromboembolism (including pulmonary embolism): Available clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs. In patients, with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman et al. 1995 and Schulman et al. 1997).

Atrial Fibrillation: Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients.

Post-Myocardial Infarction: In post myocardial infarction patients, warfarin sodium tablets, USP therapy should be initiated early (2-4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5-3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of warfarin sodium tablets, USP therapy at the lower end of this INR range is recommended.

Mechanical and Bioprosthetic Heart Valves: In patients with mechanical heart valve(s), long term prophylaxis with warfarin to an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

Recurrent Systemic Embolism: In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage: The dosing of crystalline warfarin sodium must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Low initiation doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to warfarin sodium tablets, USP (see PRECAUTIONS). It is recommended that warfarin sodium tablets, USP therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose: The anticoagulant effect of warfarin sodium tablets, USP persists beyond 24 hours. If the patient forgets to take the prescribed dose of warfarin sodium tablets, USP at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Intravenous Route of Administration: Warfarin sodium for injection provides an alternative administration route for patients who cannot receive oral drugs. The IV dosage would be the same as those that would be used orally if the patient could take the drug by the oral route.

Laboratory Control: The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin sodium tablets, USP in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

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A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained with the International Reference Preparation (IRP), which has an ISI of 1.0, were used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: $INR = (\text{observed PT ratio})^{ISI}$
where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[2-4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.[5]

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

	PT RATIOS				
	ISI 1.0	ISI 1.4	ISI 1.8	ISI 2.3	ISI 2.8
INR = 2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR = 2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

TREATMENT DURING DENTISTRY AND SURGERY The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of warfarin sodium tablets, USP to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of warfarin therapy. When discontinuing warfarin even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of warfarin sodium tablets, USP is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to warfarin sodium tablets, USP may begin concomitantly with heparin therapy or may be delayed 3 to 5 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that warfarin sodium tablets, USP therapy be overlapped with heparin for 4 to 5 days, until warfarin sodium tablets, USP has produced the desired therapeutic response as determined by PT/INR. When warfarin sodium tablets, USP has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

Warfarin sodium tablets, USP may increase the aPTT test, even in the absence of heparin. During initial therapy with warfarin sodium tablets, USP, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and warfarin sodium tablets, USP should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

Warfarin Sodium Tablets, USP: For oral use, single scored, imprinted numerically and packaged in bottles with potencies, colors and engravings as follows:

	Color	Engraving	Bottles of 100	Bottles of 1000
1 mg	Pink	T31	NDC 51672-4027-1	NDC 51672-4027-3
2 mg	Lavender	T32	NDC 51672-4028-1	NDC 51672-4028-3
2.5 mg	Green	T33	NDC 51672-4029-1	NDC 51672-4029-3
3 mg	Tan	T38	NDC 51672-4030-1	NDC 51672-4030-3
4 mg	Blue	T34	NDC 51672-4031-1	NDC 51672-4031-3
5 mg	Peach	T35	NDC 51672-4032-1	NDC 51672-4032-3
6 mg	Greenish-Yellow	T39	NDC 51672-4033-1	NDC 51672-4033-3
7.5 mg	Yellow	T36	NDC 51672-4034-1	
10 mg	White	T37	NDC 51672-4035-1	

Warfarin Sodium Tablets, USP are available in 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg of warfarin sodium, USP. They are flat beveled capsule shaped tablets, scored on one side and engraved, as described in the above table, on the other side.

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

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1. Poller, L.: Laboratory Control of Anticoagulant Therapy. Seminars in Thrombosis and Hemostasis, Vol. 12, No. 1, pp. 13-19, 1986.
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4. Hirsh, J., Dalen, J., Deykin, D., Poller, L.: Oral Anticoagulants Mechanism of Action, Clinical effectiveness, and Optimal Therapeutic Range. Chest, ACCP Consensus Conference on Antithrombotic Therapy. Vol.102(suppl), pp. 312s-326s, 1992.
5. Hirsh, J., M.D., F.C.C.P.: Hamilton Civic Hospitals Research Center, Hamilton, Ontario, Personal Communication.

Mfd. by: Taro Pharmaceutical Industries Ltd., Haifa Bay, Israel 26110 Issued: May 1999

89714-0599

[redacted]

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

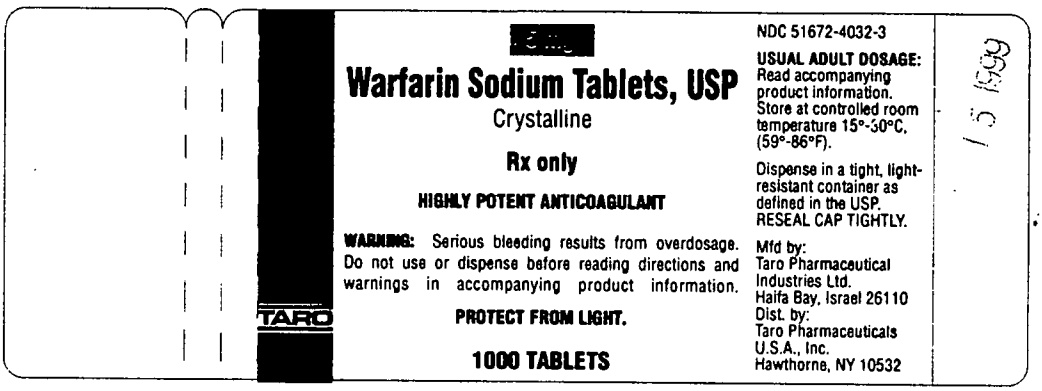
1000 TABLETS

NDC 51672-4033-3

USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532


Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
1000 TABLETS
TARO
NDC 51672-4032-3
USUAL ADULT DOSAGE: Read accompanying product information.
Store at controlled room temperature 15°-30°C. (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.
Mfd by:
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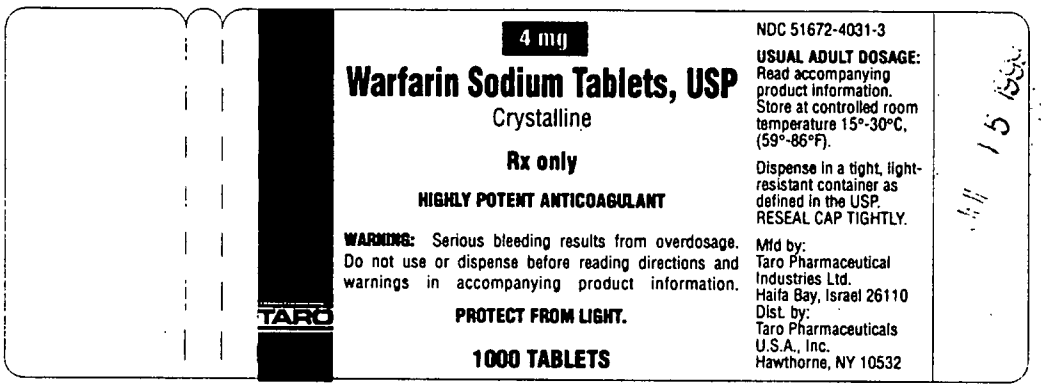

4 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

1000 TABLETS

TARO

NDC 51672-4031-3

USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

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Hawthorne, NY 10532

mango

3 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

1000 TABLETS

TARO

NDC 51672-4030-3

USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

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Hawthorne, NY 10532

2.5 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

1000 TABLETS

TARO

NDC 51672-4029-3

USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.

Mfd by:
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Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

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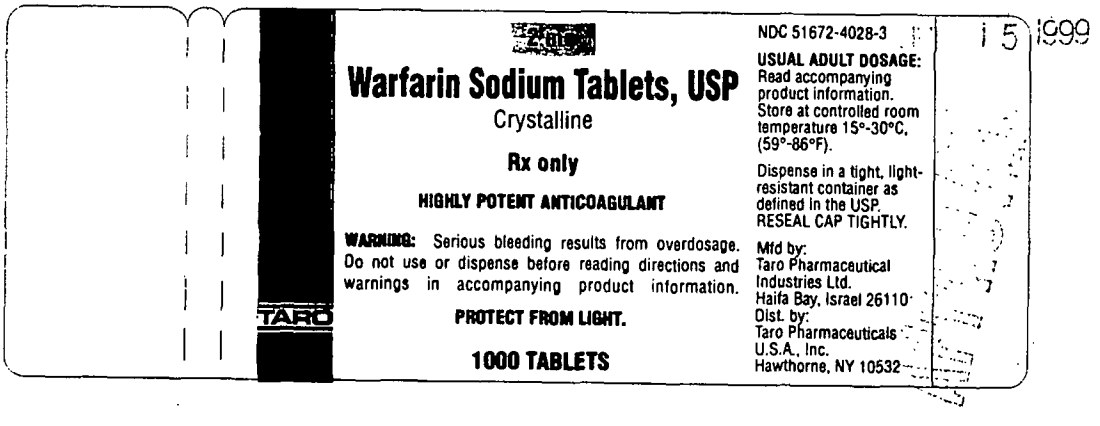


Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

1000 TABLETS

NDC 51672-4028-3

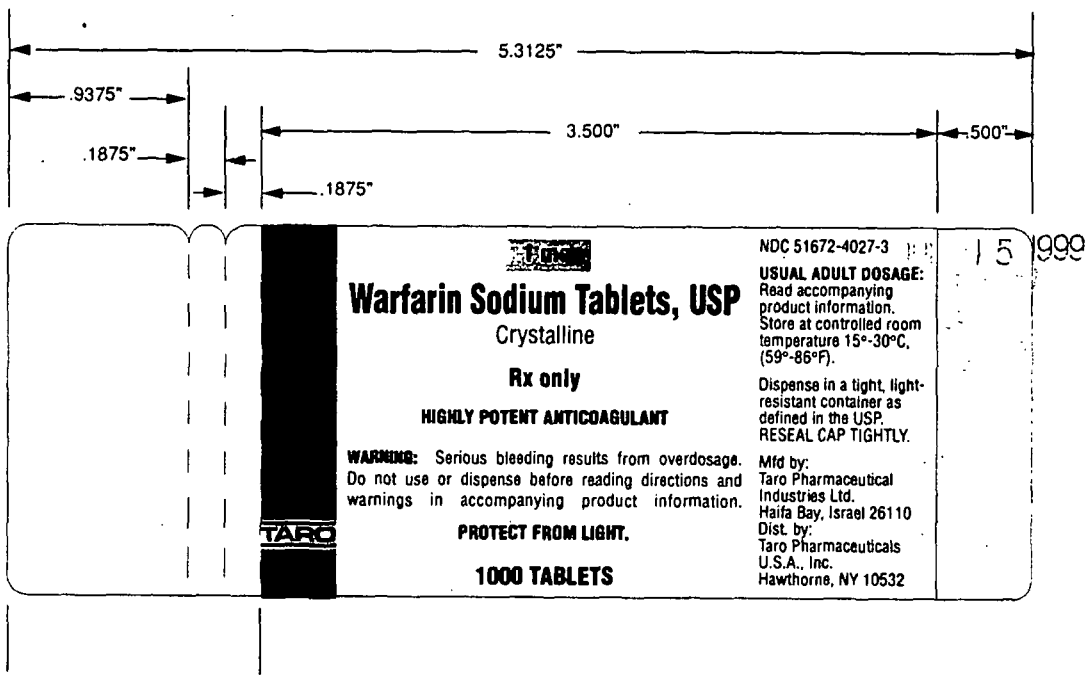
USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

TARO

15 1999


5.3125"
.9375"
.1875"
3.500"
.500"
.1875"
Rx only
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
1000 TABLETS
TARO
NDC 51672-4027-3
USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
15
999

10 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

100 TABLETS

TARO

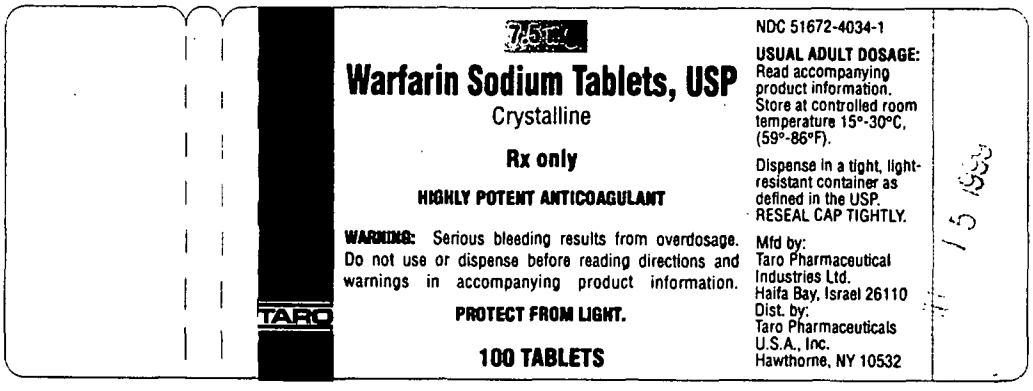
NDC 51672-4035-1

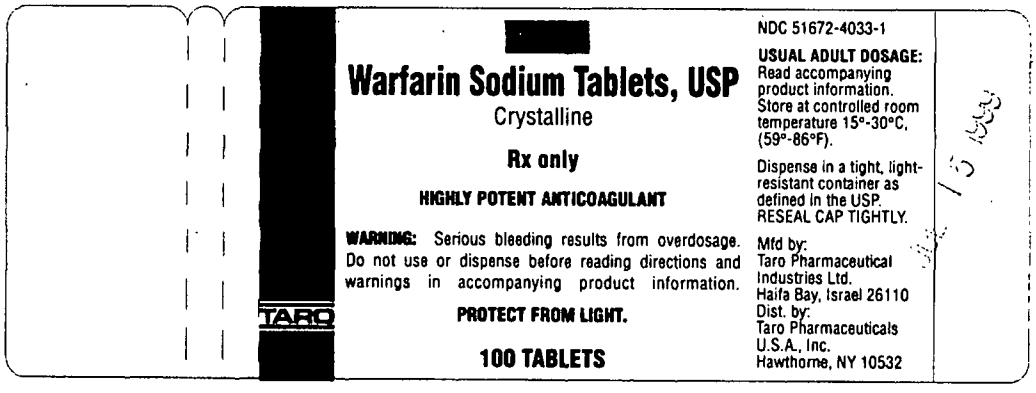
USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

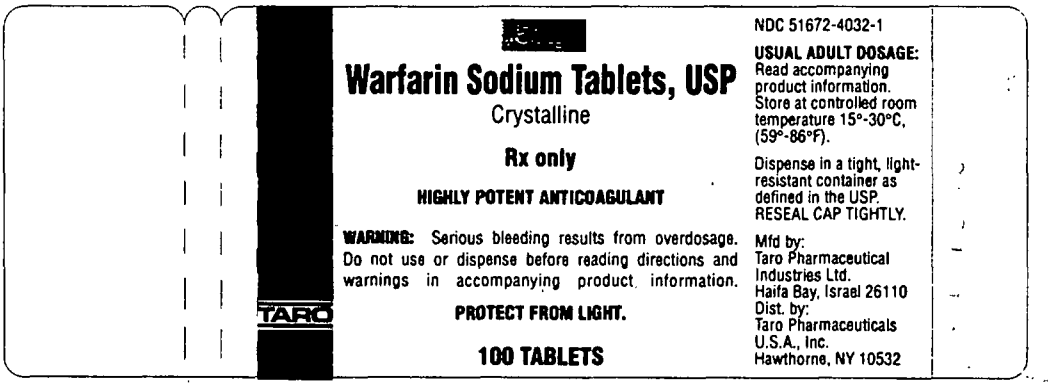
Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

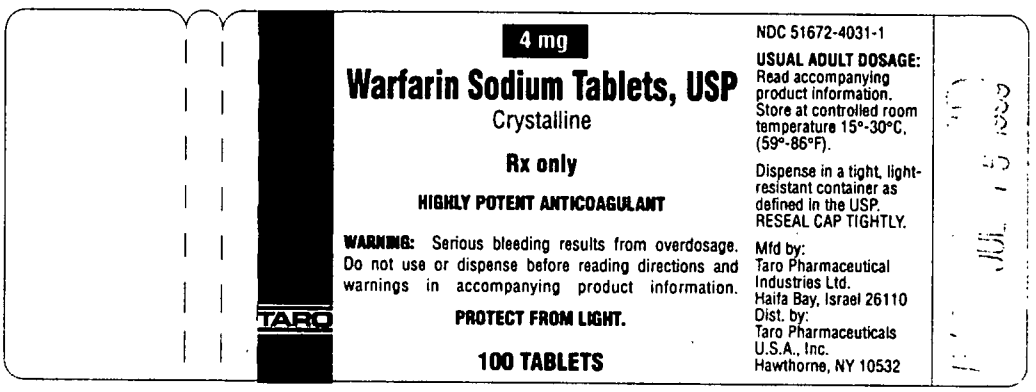
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

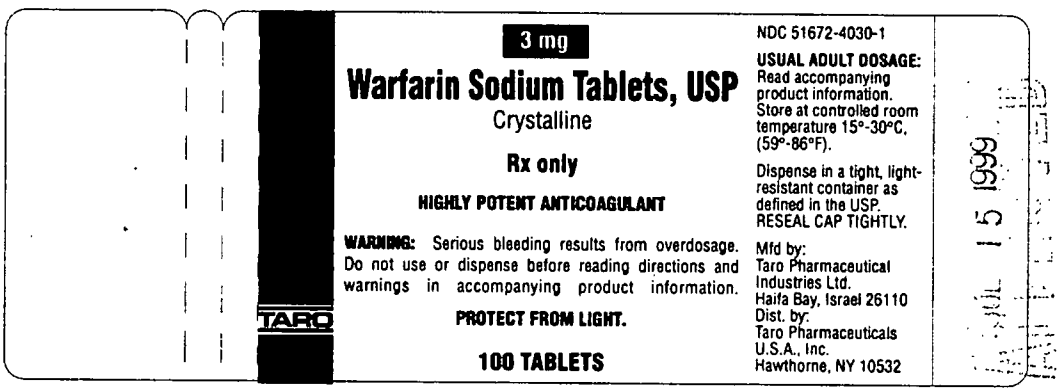
Margi


TARO
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
NDC 51672-4034-1
USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532


TARO
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
NDC 51672-4033-1
USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532


Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
TARO
NDC 51672-4032-1
USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532


4 mg
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
TARO
NDC 51672-4031-1
USUAL ADULT DOSAGE: Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532



3 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

100 TABLETS

NDC 51672-4030-1

USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.

Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

JUL 15 1999

mango

2.5 mg

Warfarin Sodium Tablets, USP

Crystalline

Rx only

HIGHLY POTENT ANTICOAGULANT

WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.

PROTECT FROM LIGHT.

100 TABLETS

NDC 51672-4029-1

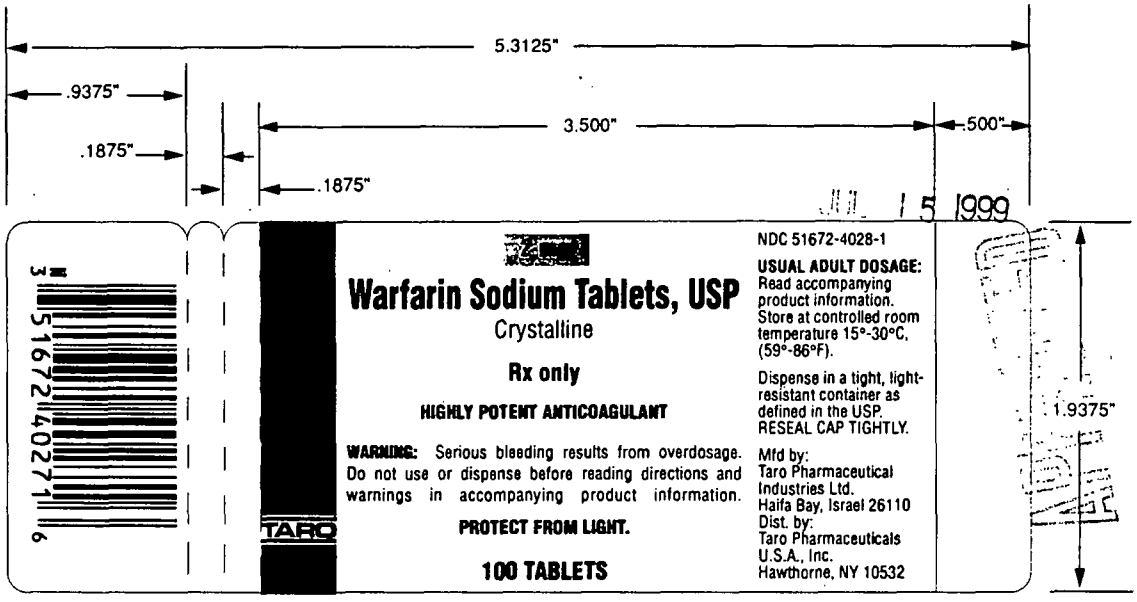
USUAL ADULT DOSAGE. Read accompanying product information. Store at controlled room temperature 15°-30°C, (59°-86°F).

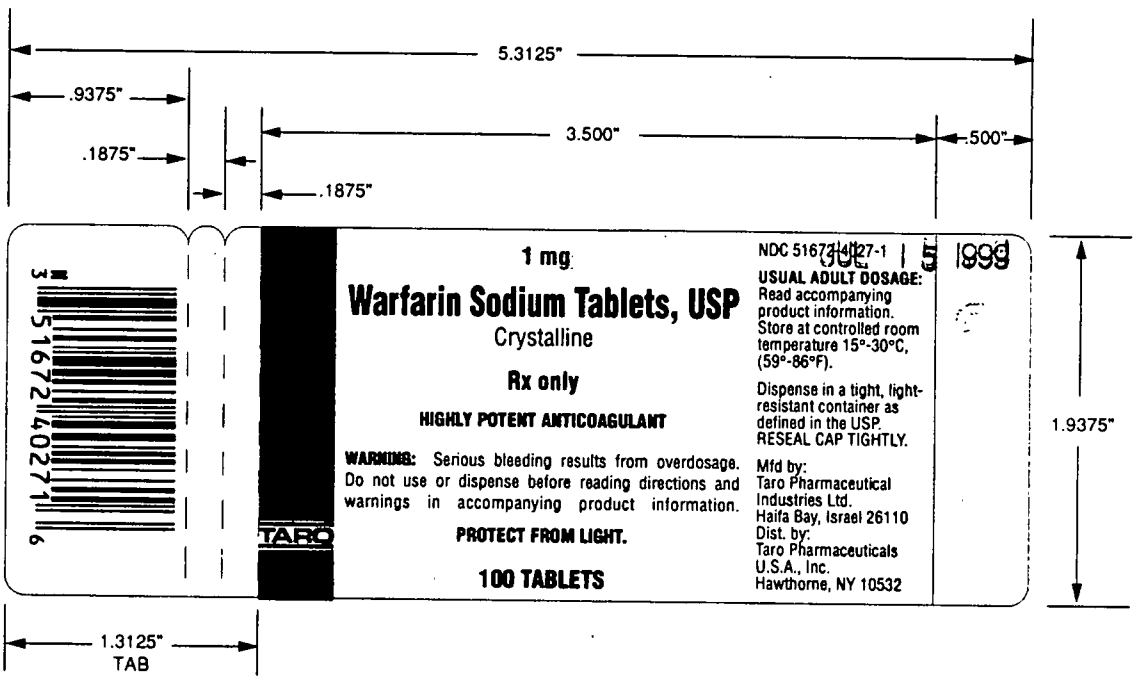
Dispense in a tight, light-resistant container as defined in the USP. RESEAL CAP TIGHTLY.

Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532

1 5 1999

margo


5.3125"
.9375"
.1875"
3.500"
.500"
.1875"
JUL 15 1999
3 51672402771 6
TARO
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
NDC 51672-4028-1
USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
1.9375"


5.3125"
.9375"
.1875"
3.500"
.500"
.1875"
3 51672 40271 6
1 mg
Warfarin Sodium Tablets, USP
Crystalline
Rx only
HIGHLY POTENT ANTICOAGULANT
WARNING: Serious bleeding results from overdosage. Do not use or dispense before reading directions and warnings in accompanying product information.
PROTECT FROM LIGHT.
100 TABLETS
TARO
NDC 51672-4027-1
USUAL ADULT DOSAGE:
Read accompanying product information.
Store at controlled room temperature 15°-30°C, (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
RESEAL CAP TIGHTLY.
Mfd by:
Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110
Dist. by:
Taro Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
JUL 5 1999
1.9375"
1.3125"
TAB