

ZyGenerics

Warfarin Sodium Tablets, USP

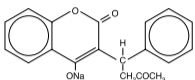
Rx only

Anticoagulant

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.

DESCRIPTION

Warfarin sodium tablet (crystalline warfarin sodium) is an anticoagulant, which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(4-oxo-5-phenyl-4H-pyridazin-3(1H)-yl)-4-hydroxycoumarin and is a racemic mixture of the R- and S-enantiomers. Crystalline warfarin sodium is an isopropanol dihydrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin.



Crystalline warfarin sodium occurs as a white crystalline powder, odorless or practically odorless. Each warfarin sodium tablet intended for oral administration contains warfarin sodium chydrate equivalent to 1 mg or 2 mg or 2.5 mg or 3 mg or 4 mg or 5 mg or 6 mg or 7.5 mg or 10 mg of warfarin sodium.

Each warfarin sodium tablet contains the inactive ingredients hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and pregelatinized starch. Additionally each 1 mg tablet contains D&C red no. 6 barium lake, 2 mg tablet contains FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake, 2.5 mg tablet contains D&C yellow no. 10 aluminum lake and FD&C blue no. 1 aluminum lake, 3 mg tablet contains FD&C yellow no. 6 aluminum lake, FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake, 4 mg tablet contains FD&C blue no. 1 aluminum lake, 5 mg tablet contains FD&C yellow no. 6 aluminum lake, 6 mg tablet contains FD&C yellow no. 6 aluminum lake and FD&C blue no. 1 aluminum lake, 7.5 mg tablet contains D&C yellow no. 10 aluminum lake and FD&C yellow no. 6 aluminum lake and 10 mg tablet is dye free.

CLINICAL PHARMACOLOGY

Warfarin sodium tablets 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 Factor VII, Protein C, Factor IX, Protein S, and Factor 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 gamma-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, 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 anticoagulation effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 3 days. The effects of warfarin sodium tablets may be 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.

Absorption:

Warfarin sodium tablet 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. Warfarin sodium tablets are 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 diastereoisomeric alcohols, 4-, 6-, 7-, 8- and 10-hydroxywarfarin. The cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the in vivo anticoagulant activity of warfarin.

Excretion:

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

Elderly:

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

Asians:

Asian patients may require lower initiation and maintenance doses of warfarin. One non-controlled study conducted in 151 Chinese outpatients reported a mean daily warfarin requirement of 3.3 ± 1.4 mg to achieve an INR of 2 to 2.5. These patients were stabilized on warfarin for various indications. Patient history and physical examination revealed a lower requirement in Chinese patients with a progressively lower warfarin requirement with increasing age.

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 non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (see Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CASA; 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 of these trials (see Table 1) 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

Table with 7 columns: Study, N, Warfarin-Treated Patients, Control Patients, PT Ratio, INR, % Risk Reduction, p-value, Warfarin-Treated Patients, Control Patients. Rows include AFASAK, SPAF, BAATAF, CAFA, SPINAF.

*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 II (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 INRs 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

Table with 5 columns: Event, Warfarin (N=607), Placebo (N=607), RR (95% CI), % Risk Reduction (p-value). Rows include Total Patient Years of Follow-up, Total Mortality, Vascular Death, Recurrent MI, Cerebrovascular Event.

RR= Relative risk; Risk reduction = (1 - RR); CI=Confidence interval; MI=Myocardial infarction; py = patient years
WARIS II (The Warfarin, Aspirin, Re-Infarction Study) was an open-label randomized study of 3630 patients hospitalized for acute myocardial infarction treated with warfarin target INR 2.8 to 4.2, aspirin 160 mg/day, or warfarin target INR 2.0 to 2.5 plus aspirin 75 mg/day prior to hospital discharge. There were approximately four times as many major bleeding episodes in the two groups receiving warfarin than in the group receiving aspirin alone. Major bleeding episodes were not more frequent among patients receiving aspirin plus warfarin than among those receiving warfarin alone, but the incidence of minor bleeding episodes was higher in the combined therapy group. The primary endpoint was a composite of death, nonfatal reinfarction, or thromboembolic stroke. The mean duration of observation was approximately 4 years. The results for WARIS II are provided in the following table:

TABLE 3

Table with 6 columns: Event, Aspirin (N=1206), Warfarin (N=1216), Aspirin plus Warfarin (N=1208), Rate Ratio (95% CI), p-value. Rows include Reinfarction, Thromboembolic stroke, Major Bleeding, Minor Bleeding, Death.

* CI denotes confidence interval.
The rate ratio is for aspirin plus warfarin as compared with aspirin.
The rate ratio is for warfarin as compared with aspirin.
Major bleeding episodes were defined as nonfatal cerebral hemorrhage or bleeding necessitating surgical intervention.
Minor bleeding episodes were defined as non-cerebral hemorrhage not necessitating surgical intervention of blood transfusion.
ND = not determined.

Mechanical and Bioprosthetic Heart Valves:

In a prospective, randomized, open label, positive-controlled study* 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 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 in 210 patients comparing two intensities of warfarin therapy (INR 2.0-2.25 vs. INR 2.5-4.0) for a three-month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (major hemorrhages 4.6% vs. none in the lower intensity.*

INDICATIONS AND USAGE

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

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

Warfarin sodium tablets 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 are contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fetal 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 defect and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft lip, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and stillbirth 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 these risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of:

(1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of:

(1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation. Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous:

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

WARNINGS

The most serious risks associated with anticoagulant therapy with warfarin sodium are hemorrhage in any tissue or organ* (see BLACK BOX WARNING) and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. Hemorrhage and necrosis have in some cases been reported and may be life threatening. 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 dietary vitamin K. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and warfarin sodium tablets are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Caution should be observed when warfarin sodium tablets are 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 sodium tablets 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 sodium tablets 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, central 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 the 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 sodium tablets should be used with caution in patients with heparin-induced thrombocytopenia and deep vein thrombosis. Cases of venous limb ischemic necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep vein 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.* A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

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

Lactation:

Based on a 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 some breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times, although not as prolonged as those of the mothers. 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 PT/INR values are not exceeded. It is prudent to perform coagulation tests and to evaluate vitamin K status in infants at risk for bleeding tendencies before advising women taking warfarin to breast-feed. 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 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.

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 sodium tablets 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 tablets, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium 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/INR or other suitable coagulation test is essential (see DOSAGE AND ADMINISTRATION; LABORATORY CONTROL).

Drug-Drug and Drug-Disease Interactions

Numerous factors, alone or in combination, including changes in diet and medications, including botanicals, 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, including botanicals, are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interfere with warfarin sodium tablets 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.

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

ENDOGENOUS FACTORS:

Table with 3 columns: 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 tablets are listed below by drug class and by specific drugs.

Table with 3 columns: Classes of Drugs, Antiplatelet Drugs/Effects, Leukotriene Receptor Antagonist. Lists various drug classes and their interactions with warfarin.

Specific Drugs Reported:

Table with 3 columns: Specific Drugs Reported, Specific Drugs Reported, Specific Drugs Reported. Lists specific drugs and their interactions with warfarin.

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:

Table with 2 columns: edema, hereditary coumarin resistance, hyperlipemia, hypothyroidism, nephrotic syndrome.

EXOGENOUS FACTORS:

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

Table with 3 columns: Classes of Drugs, Antipsychotic Medications, Hypolipidemics. Lists various drug classes and their interactions with warfarin.

Specific Drugs Reported:

Table with 3 columns: Specific Drugs Reported, Specific Drugs Reported, Specific Drugs Reported. Lists specific drugs and their interactions with warfarin.

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 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.

Botanical (Herbal) Medicines:

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

Specific botanicals reported to affect warfarin sodium tablets therapy include the following:

- Bromelains, danshen, dong quai (Angelica sinensis), garlic, Ginkgo biloba, ginseng, and cranberry products are associated most often with an INCREASE in the effects of warfarin sodium tablets.
Coenzyme Q10 (ubidecarenone) and St. John's wort are associated most often with a DECREASE in the effects of warfarin sodium tablets.

Some botanicals 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 botanicals may have coagulant properties when taken alone or may decrease the effects of warfarin sodium tablets.

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed.

Table with 3 columns: Botanicals that contain coumarins with potential anticoagulant effects: Alfalfa, Angelica (Dong Quai), Aniseed, Celery, Chamomile, Parsley, Passion Flower, Prickly Ash (Northern).

Amica	Dandelion ³	Quassia
Asa Foetida	Fenugreek	Red Clover
Bogbean ¹	Horse Chestnut	Sweet Clover
Boldo	Horseradish	Sweet Woodruff
Buchu	Licorice ³	Tonka Beans
Capsicum ²	Meadowsweet ¹	Wild Carrot
Cassia ³	Nettle	Wild Lettuce
Miscellaneous botanicals with anticoagulant properties:		
Bladder Wrack (<i>Fucus</i>)	Pau d'arco	-
Botanicals that contain salicylate and/or have antiplatelet properties:		
Agrimony ⁴	Dandelion ³	Meadowsweet ¹
Alce Gel	Feverfew	Onion ⁵
Aspen	Garlic ⁶	Policosanol
Black Cohosh	German Sarsaparilla	Poplar
Black Haw	Ginger	Senega
Bogbean ¹	Ginkgo Biloba	Tamarind
Cassia ³	Ginseng (<i>Panax</i>) ⁷	Willow
Clove	Licorice ³	Wintergreen
Botanicals with fibrinolytic properties:		
Bromelains	Garlic ⁶	Inositol Nicotinate
Capsicum ²	Ginseng (<i>Panax</i>) ⁷	Onion ⁵
Botanicals with coagulant properties:		
Agrimony ⁴	Mistletoe	
Goldenseal	Yarrow	

¹Contains coumarins and salicylate.

²Contains coumarins and has fibrinolytic properties.

³Contains coumarins and has antiplatelet properties.

⁴Contains salicylate and has coagulant properties.

⁵Has antiplatelet and fibrinolytic properties.

Effect on Other Drugs:

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

Special Risk Patients:

Warfarin sodium 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 sodium tablets are 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 sodium tablets 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), other over-the-counter medications, and botanical (herbal) products (e.g., bromelains, coenzyme Q₁₀, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John's wort) except on advice of the physician. Avoid alcohol consumption. Do not take warfarin sodium tablets 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 sodium tablets are being taken. If the prescribed dose of warfarin sodium tablets 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 sodium tablets the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with warfarin sodium tablets. 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. You should also avoid intake of cranberry juice or any other cranberry products. Notify your health care provider if any of these products are part of your normal diet. 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 sodium tablets is discontinued, patients should be cautioned that anticoagulant effects of warfarin sodium tablets may persist for about 2 to 5 days. **Patients should be informed that all warfarin sodium, USP products represent the same medication, and should not be taken concomitantly, as overdosage may result.** A Medication Guide¹ should be available to patients when their prescriptions for warfarin sodium are issued.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity and mutagenicity studies have not been performed with warfarin sodium tablets. The reproductive effects of warfarin sodium tablets 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 sodium tablets in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

Geriatric Use:

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see **CLINICAL PHARMACOLOGY**). Warfarin sodium tablets are contraindicated in any unsupervised patient with senility. Caution should be observed when administration of warfarin sodium to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Lower initiation and maintenance doses of warfarin sodium tablets are recommended for elderly patients (see **DOSE AND ADMINISTRATION**).

ADVERSE REACTIONS

Potential adverse reactions to warfarin sodium tablets 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, hypotension, vasculitis, edema, anemia, pallor, fever, rash, dermatitis, including hives eruptions, urticaria, angina syndrome, chest pain, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, loss of consciousness, syncope, coma, taste perversion, pruritus, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

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

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

OVERDOSAGE

Signs and Symptoms:

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

Treatment:

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing warfarin sodium tablets therapy and if necessary, by administration of oral or parenteral vitamin K. (Please see recommendations accompanying vitamin K, preparations prior to use.)^{8,9}

Such use of vitamin K, reduces response to subsequent warfarin sodium tablets therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of warfarin sodium 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. 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 sodium overdosage.

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

DOSE AND ADMINISTRATION

The dosage and administration of warfarin sodium tablets 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.^{8,9,10,11,12} **The best available information supports the following recommendations for dosing of warfarin sodium 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 recommended. For patients with a first episode of idiopathic DVT or PE, warfarin is 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 a first episode of DVT or PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions, treatment for 12 months is recommended and indefinite therapy is suggested. For patients with a first episode of DVT or PE who have documented deficiency of antithrombin, deficiency of Protein C or Protein S, or the Factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high Factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended and indefinite therapy is suggested for idiopathic thrombosis. The risk-benefit should be reassessed periodically in patients who receive indefinite anticoagulant treatment.¹³ 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. These recommendations are supported by the 7th ACCP guidelines.^{8,9,10,14,15}

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. There are no adequate and well-controlled studies in populations with atrial fibrillation and valvular heart disease. 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' (7th ACCP) recommendation that an INR of 2.0-3.0 be used for warfarin therapy in appropriate AF patients.¹⁰

Oral anticoagulation therapy with warfarin is recommended in patients with persistent or paroxysmal AF (PAF) (intermittent AF) at high risk of 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 and/or congestive heart failure, history of hypertension, or diabetes mellitus). In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, but who are at intermediate risk of stroke, antithrombotic therapy with either oral warfarin or aspirin, 325 mg/day, is recommended. For patients with AF and mitral stenosis, anticoagulation with oral warfarin is recommended (7th ACCP). For patients with AF and prosthetic heart valves, anticoagulation with oral warfarin should be used; the target INR may be increased and aspirin added depending on valve type and position, and on patient factors.¹⁶

Post-Myocardial Infarction:

The results of the WARIS II study and 7th ACCP guidelines suggest that in most healthcare settings, moderate- and low-risk patients with a myocardial infarction should be treated with aspirin alone over oral vitamin-K antagonist (VKA) therapy plus aspirin. In healthcare settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after myocardial infarction (MI), long-term (up to 4 years) high-intensity oral warfarin (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral warfarin (target INR, 2.5; range, 2.0 to 3.0) with aspirin is recommended. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, therapy with combined moderate-intensity (INR, 2.0 to 3.0) oral warfarin plus low-dose aspirin (≤100 mg/day) for 3 months after the MI is suggested.¹⁴

Mechanical and Bioprosthetic Heart Valves:

For all patients with mechanical prosthetic heart valves, warfarin is recommended. For patients with a St. Jude Medical (St. Paul, MN) bileaflet valve in the aortic position, a target INR of 2.5 (range, 2.0 to 3.0) is recommended. For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, the 7th ACCP recommends a target INR of 3.0 (range, 2.5 to 3.5). For patients with caged ball or caged disk valves, a target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/day is recommended. For patients with bioprosthetic valves, warfarin therapy with a target INR of 2.5 (range, 2.0 to 3.0) is recommended for valves in the mitral position and is suggested for valves in the aortic position for the first 3 months after valve insertion.⁸

Recurrent Systemic Embolism and Other Indications:

Oral anticoagulation therapy has not been evaluated by properly designed clinical trials in patients with valvular disease associated with atrial fibrillation, patients with mitral stenosis, and patients with recurrent systemic embolism of unknown etiology. A moderate dose regimen (INR 2.0 to 3.0) is recommended for these patients.¹⁰

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 warfarin sodium tablets 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. Lower initiation and maintenance 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 (see **PRECAUTIONS**). Based on limited data, Asian patients may also require lower initiation and maintenance doses of warfarin sodium tablets (see **CLINICAL PHARMACOLOGY**). It is recommended that warfarin sodium 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.^{8,9,11}

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.^{7,8,10,11,14,15}

Missed Dose:

The anticoagulant effect of warfarin sodium tablets persists beyond 24 hours. If the patient forgets to take the prescribed dose of warfarin sodium 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.

LABORATORY CONTROL:

The PT reflects the depression of vitamin K dependent Factors VII, X, and II. A system of standardizing the PT in oral anticoagulant therapy 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.¹⁷ **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 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 be 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).** 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, among self-testing and self-monitoring patients, and in patients managed by a team of computer programs.¹⁸ Self-testing patients had fewer bleeding events than patients in usual care.¹⁸

TREATMENT DURING DENTISTRY AND SURGERY:

The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists.^{8,12} 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 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 sodium tablets therapy. When discontinuing warfarin sodium 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 warfarin sodium tablets is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to warfarin sodium 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 warfarin sodium tablets therapy be overlapped with heparin for 4 to 5 days, until warfarin sodium tablets have produced the desired therapeutic response as determined by PT/INR. When warfarin sodium tablets have produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

Warfarin sodium tablets may increase the aPTT test, even in the absence of heparin. During initial therapy with warfarin sodium tablets, 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 should have blood for PT/INR determination drawn at least:

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

HOW SUPPLIED

Warfarin Sodium Tablets, 1 mg are pink, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '1' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-052-01 in bottles of 100 tablets
NDC 68382-052-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 2 mg are lavender, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '2' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-053-01 in bottles of 100 tablets
NDC 68382-053-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 2.5 mg are green, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '2½' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-064-01 in bottles of 100 tablets
NDC 68382-064-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 3 mg are tan, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '3' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-054-01 in bottles of 100 tablets
NDC 68382-054-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 4 mg are blue, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '4' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-055-01 in bottles of 100 tablets
NDC 68382-055-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 5 mg are peach, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '5' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-056-01 in bottles of 100 tablets
NDC 68382-056-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 6 mg are teal, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '6' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-057-01 in bottles of 100 tablets
NDC 68382-057-10 in bottles of 1000 tablets

Warfarin Sodium Tablets, 7.5 mg are yellow, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '7½' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-058-01 in bottles of 100 tablets

Warfarin Sodium Tablets, 10 mg are white to off white, oval, flat, beveled edge, uncoated tablets debossed with the logo of "WAR", '10' and bisect on one side and plain on other side and are supplied as follows:

NDC 68382-059-01 in bottles of 100 tablets

Storage

Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. Protect from light. Dispense in a tight, light-resistant container as defined in the USP.

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Medication Guide Warfarin Sodium Tablets, USP

[Rx only]

Read this Medication Guide before you start taking Warfarin Sodium Tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about warfarin sodium tablets when you start taking it and at regular checkups.

What is the most important information I should know about warfarin sodium tablets?

- Take your warfarin sodium tablets exactly as prescribed to lower the chance of blood clots forming in your body (see "What is warfarin sodium?").

- Warfarin sodium tablets are very important for your health, but it can cause serious and life-threatening bleeding problems. To benefit from warfarin sodium tablets and also lower your chance for bleeding problems, you must:

- Get your regular blood test to check for your response to warfarin sodium tablets.

This blood test is called a PT/INR test. The PT/INR test checks to see how fast your blood clots. Your healthcare provider will decide what PT/INR numbers are best for you. Your dose of warfarin sodium tablets will be adjusted to keep your PT/INR in a target range for you.

- Call your healthcare provider right away if you get any of the following signs or symptoms of bleeding problems:

- pain, swelling or discomfort
- headaches, dizziness, or weakness
- unusual bruising (bruises that develop without known cause or grow in size)
- nose bleeds
- bleeding gums
- bleeding from cuts takes a long time to stop
- menstrual bleeding or vaginal bleeding that is heavier than normal
- pink or brown urine
- red or black stools
- coughing up blood
- vomiting blood or material that looks like coffee grounds