

# JANTOVEN® TABLETS

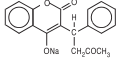
## (Warfarin Sodium Tablets, USP)

### WARNING: BLEEDING RISK

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

### DESCRIPTION

Jantoven® Tablets (crystalline warfarin sodium) is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(4-acetyloxyphenyl)-4-hydroxyquinoline 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. Its empirical formula is  $C_{19}H_{15}NaO_4$ , 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.

Jantoven® Tablets (Warfarin Sodium Tablets, USP) for oral use contain: 1 mg, 2 mg, 2 1/2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 1/2 mg or 10 mg of crystalline warfarin sodium, USP. They also contain:

All Strengths: Lactose monohydrate, magnesium stearate, povidone, and pregelatinized starch (corn).

1 mg: FD&C Red #40 Aluminum Lake  
2 mg: FD&C Blue #2 Aluminum Lake and FD&C Red #40 Aluminum Lake  
2 1/2 mg: D&C Yellow #10 Aluminum Lake and FD&C Blue #1 Aluminum Lake  
3 mg: Brown #75 Synthetic Brown Iron Oxide  
4 mg: FD&C Blue #1 Aluminum Lake  
5 mg: FD&C Yellow #6 Aluminum Lake  
6 mg: Yellow #10 Synthetic Yellow Iron Oxide, Black #85 Synthetic Black Iron Oxide and FD&C Blue #1 Aluminum Lake  
7 1/2 mg: D&C Yellow #10 Aluminum Lake and FD&C Yellow #6 Aluminum Lake  
10 mg: Dye Free.

### CLINICAL PHARMACOLOGY

Jantoven® Tablets (Warfarin Sodium Tablets, USP) 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 essential *in vivo* effect to 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-translational 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.

### Mechanism of Action

Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K<sub>1</sub> epoxide. The degree of depression is dependent upon the dosage administered and, in part, by the essential VKORC1 genotype. 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 5 days. The effects of Jantoven® Tablets 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

Jantoven® Tablets are 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

Jantoven® Tablets are 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 sodium. 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. Jantoven® 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 C2C9, 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.

The S-enantiomer of warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles CYP2C9\*2 and CYP2C9\*3 result in decreased *in vitro* CYP2C9 enzymic 7-hydroxylation of S-warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9\*2 and CYP2C9\*3, respectively<sup>1</sup>. Patients with one or more of these variant CYP2C9 alleles have decreased S-warfarin clearance (Table 1).<sup>2</sup>

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

<sup>1</sup>SD=standard deviation

<sup>2</sup>p<0.001. Pairwise comparisons indicated significant differences among all 3 genotypes

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

### Pharmacogenomics

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

In an observational study, the risk of achieving INR-3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype. The relative risk of over anticoagulation as measured by INR-3 during the first 2 weeks of therapy was approximately doubled for those patients classified as \*2 or \*3 compared to patients who were homozygous for the \*1 allele.<sup>4</sup>

Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (especially the 1639G:A allele) have been associated with lower dose requirements for warfarin. In 2011 Caucasian patients treated with stable

warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses. In this study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in CYP2C9 and CYP2C9 genes combined.<sup>5</sup> About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients.<sup>5</sup> Similar observations have been reported in Asian patients.<sup>6</sup>

### Excitation

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 age was not the most important determinant of warfarin 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 2**). 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 studies. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (see **Table 2**). 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.

Study	N		Thromboembolism			% Major Bleeding		
	Treated Patients	Control Patients	PT	INR	% Risk Reduction	Treated Patients	Control Patients	
AFASAC	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
CATAF	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 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 **DOSE 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:

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	11 (0.1/00 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

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:

Event	Aspirin plus Warfarin (N=1206)		Warfarin (N=1216)		Aspirin (N=1208)		Rate Ratio (95% CI)	p-value
	No. of Events	No. of Events	No. of Events	No. of Events	No. of Events			
Reinfarction	117	90	69	0.56 (0.41-0.78) <sup>a</sup>	<0.001			
Thromboembolic stroke	32	17	17	0.52 (0.28-0.98) <sup>b</sup>	0.03			
Major Bleeding <sup>c</sup>	8	33	28	0.52 (0.28-0.97) <sup>b</sup>	0.03			
Minor Bleeding <sup>d</sup>	39	103	133	3.21 (ND)	ND			
Death	92	96	95	2.53 (ND)	ND			

\* CI denotes confidence interval.

<sup>a</sup> The rate ratio is for aspirin plus warfarin as compared with aspirin.

<sup>b</sup> The rate ratio is for warfarin as compared with aspirin.

<sup>c</sup> Major bleeding episodes were defined as nonfatal cerebral hemorrhage or bleeding necessitating surgical intervention, or blood transfusion.

<sup>d</sup> Minor bleeding episodes were defined as non-cerebral hemorrhage not necessitating surgical intervention or blood transfusion.

ND = not determined.

#### Mechanical and Bioprosthetic Heart Valves

In a prospective, randomized, open label, positive-controlled study<sup>7</sup> 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<0.05) and pentoxifyllin-aspirin (p<0.05) treatment 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 2.66) vs. high intensity (INR 3.0) 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.<sup>8</sup>

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).<sup>11</sup>

### INDICATIONS AND USAGE

Jantoven® Tablets (Warfarin Sodium Tablets, USP) are indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

Jantoven® Tablets are indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

Jantoven® 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

Jantoven® Tablets (Warfarin Sodium Tablets, USP) 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 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 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 those risks.

#### Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery at: (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 pre-eclampsia.

#### Inadequate laboratory facilities.

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

Spinal puncture or other diagnostic or therapeutic procedures with potential for uncontrolled 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 anticoagulation therapy with warfarin sodium are hemorrhage in any tissue or organ<sup>12</sup> (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 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 hepatic injury 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 anticoagulation 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. Jantoven® Tablets (Warfarin Sodium Tablets, USP), 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)/International Normalized Ratio (INR). 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 Jantoven® Tablets are administered concomitantly, refer below to **Conversion From Heparin Therapy** for recommendations.

Increased caution should be observed when Jantoven® Tablets are administered in the presence of any predisposing condition where added risk of hemorrhage, necrosis and/or gangrene is present.

Anticoagulation therapy with Jantoven® 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 Jantoven® Tablets therapy is recommended when such phenomena are observed.

Systemic atheroembolic 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 resembling 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.

Jantoven® Tablets 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.<sup>13</sup>

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

**Lactation:** Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that 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 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:** sparse, 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 concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with Jantoven® 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 hepatic injury may be considered for anticoagulation.

**Miscellaneous:** polythymia, vascuclitis, and severe diabetes.



## 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.<sup>23</sup>

## 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.<sup>15</sup>

## 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.<sup>17</sup>

**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 Jantoven<sup>®</sup> 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. It is recommended that Jantoven<sup>®</sup> 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.<sup>17,18</sup> The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to Jantoven<sup>®</sup> Tablets (see **CLINICAL PHARMACOLOGY and PRECAUTIONS**).

## Maintenance

Most patients are individually 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. Acquired or inherited warfarin resistance is rare, but should be suspected if large daily doses of warfarin are required to maintain a patient's PT/INR within a normal therapeutic range. Lower maintenance doses are recommended for elderly and/or debilitated patients and patients with a potential to exhibit greater than expected PT/INR response to warfarin sodium (see **PRECAUTIONS**).

## Duration of Therapy

The duration of therapy in each patient should be individualized. In general, anticoagulation therapy should be continued until the danger of thrombosis and embolism has passed.<sup>14,15,17,18,21,22</sup>

## Missed Dose

The anticoagulant effect of Jantoven<sup>®</sup> Tablets persists beyond 24 hours. If the patient forgets to take the prescribed dose of Jantoven<sup>®</sup> 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 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.<sup>24</sup> **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 Jantoven<sup>®</sup> 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 with the help of computer programs.<sup>25</sup> Self-testing patients had fewer bleeding events than patients in usual care.<sup>26</sup>

## Treatment During Dentistry And Surgery

The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists.<sup>15,19</sup> 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 Jantoven<sup>®</sup> 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 Jantoven<sup>®</sup> Tablets therapy. When discontinuing Jantoven<sup>®</sup> Tablets even for a short period of time, the benefits and risks should be thoroughly considered.

## Conversion From Heparin Therapy

Since the anticoagulant effect of Jantoven<sup>®</sup> Tablets is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to Jantoven<sup>®</sup> 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 Jantoven<sup>®</sup> Tablets therapy be overlapped with heparin for 4 to 5 days, until Jantoven<sup>®</sup> Tablets has produced the desired therapeutic response as determined by PT/INR. When Jantoven<sup>®</sup> Tablets has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

Jantoven<sup>®</sup> Tablets may increase the activated partial thromboplastin time (aPTT test) even in the absence of heparin. 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.

During initial therapy with Jantoven<sup>®</sup> Tablets, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and Jantoven<sup>®</sup> Tablets 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

Jantoven<sup>®</sup> Tablets (Warfarin Sodium Tablets, USP) for oral use, are supplied in the following forms:

- 1 mg - Compressed tablet, pink, round; one side scored and debossed WRF & 1, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 2 mg - Compressed tablet, lavender, round; one side scored and debossed WRF & 2, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 2 1/2 mg - Compressed tablet, green, round; one side scored and debossed WRF & 2 1/2, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 3 mg - Compressed tablet, tan, round; one side scored and debossed WRF & 3, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 4 mg - Compressed tablet, blue, round; one side scored and debossed WRF & 4, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 5 mg - Compressed tablet, peach, round; one side scored and debossed WRF & 5, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 6 mg - Compressed tablet, teal, round; one side scored and debossed WRF & 6, one side debossed 832, in bottles of 100 and 1000 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 7 1/2 mg - Compressed tablet, yellow, round; one side scored and debossed WRF & 7 1/2, one side debossed 832, in bottles of 100 and 500 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).
- 10 mg - Compressed tablet, white, round; one side scored and debossed WRF & 10, one side debossed 832, in bottles of 100 and 500 and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each).

Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from light and moisture. Dispense in a tight, light-resistant container with a child-resistant closure.

## Keep out of reach of children.

## Rx only

## REFERENCES

1. Yasar U, Eliasson E, Dahl M, Johansson I, Ingelman-Sundberg, M, Spjovist F. Validation of methods for CYP2C9 genotyping: Frequencies of mutant alleles in Swedish population. *Biochem Biophys Res Commun.* 1999; 254: 628-631.
2. Herman D, Locatelli I, Grabnar I, et al. Influence of CYP2C9 polymorphism, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. *Pharmacogenomics J.* 2005; 5: 193-202.
3. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: A HuGenet<sup>™</sup> systemic review and meta-analysis. *Genet Med.* 2005; 7: 97-104.
4. Lindh JD, Lundgren S, Holm L, Alfredsson L, Rane A. Several-fold increase in risk of overanticoagulation by CYP2C9 mutations. *Clin Pharmacol Ther.* 2005; 78:540-550.
5. Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GCXC polymorphisms associated with warfarin dose. *Pharmacogenomics J.* 2005; 5:262-270.
6. Veenstra DL, You JHS, Rieder MJ, et al. Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. *Pharmacogenet Genomics.* 2005;15:687-691.
7. Takahashi H, Wilkinson GR, Nutescu EA, et al. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance doses of warfarin in Japanese, Caucasians and African Americans. *Pharmacogenet Genomics.* 2006;16:101-110.
8. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med.* 2002;347:969-974.
9. Mok CK, Boey J, Wang R, et al. Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for prevention of prosthetic valve thromboembolism: a prospective randomized clinical trial. *Circ.* 1985;72:1059-1063.
10. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med.* 1990;332:428-432.
11. Turpie AG, Hirsh J, Gustensen J, Nelson H, Gent M. Randomized comparison to two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet.* 1988;331:1242-1245.
12. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:401S-428S.
13. Warkentin TE, Elavathil LJ, Hayward CPM, Johnston MG, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med.* 1997;127:804-812.
14. Jantoven<sup>®</sup> Tablets Medication Guide. Minneapolis, MN: Upsher-Smith Laboratories, Inc.; 2007.
15. Salem DH, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:457S-482S.
16. American Geriatrics Society Clinical Practice Guidelines. The use of oral anticoagulants (warfarin) in older people. *J Amer Geriatr Soc.* 2000;48:224-227.
17. Singer DE, Albers GW, Dalen JE, Go AS, Halperin LJ, Manning WJ. Antithrombotic Therapy in Atrial Fibrillation. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:429S-456S.
18. Jaffer AK, Bragg L. Practical tips for warfarin dosing and monitoring. *Cleveland Clinic J Med.* 2003;70:361-371.
19. Jaffer AK, Brotman DJ, Chukunmerije H. When patients on warfarin need surgery. *Cleveland Clinic J Med.* 2003;70:973-984.
20. Keaton C, Ginsberg JS, Kovacs MJ, et al, for the Extended Low-Intensity Anticoagulation for Thrombo-Embolic Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;349:631-639.
21. Schulman S, Granqvist S, Holmström M, et al, The Duration of Oral Anticoagulant Trial Study Group. The duration of oral anticoagulation therapy after a second episode of venous thromboembolism. *N Engl J Med.* 1997;336:393-398.
22. Ridker PM, Goldhaber SZ, Danielson E, et al, for the PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;348:1425-1434.
23. Harrington RA, Becker RC, Ezekowitz M, et al. Antithrombotic therapy for coronary artery disease. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:513S-548S.
24. Ansell J, Hirsh J, Pollen L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:204S-233S.
25. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet.* 2006;367:404-411.

Manufactured by

UPSHER-SMITH LABORATORIES, INC.

Minneapolis, MN 55447

JAP05-00

Revised 0807

## Medication Guide Jantoven<sup>®</sup> (JAN-to-ven) Tablets (Warfarin Sodium Tablets, USP)

Read this Medication Guide before you start taking Jantoven<sup>®</sup> Tablets (Warfarin Sodium Tablets, USP) 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 Jantoven<sup>®</sup> Tablets when you start taking it and at regular checkups.

## What is the most important information I should know about Jantoven<sup>®</sup> Tablets?

- **Take your Jantoven<sup>®</sup> Tablets exactly as prescribed to lower the chance of blood clots forming in your body.** (See “What are Jantoven<sup>®</sup> Tablets?”).
- **Jantoven<sup>®</sup> Tablets are very important for your health, but it can cause serious and life-threatening bleeding problems.** To benefit from Jantoven<sup>®</sup> Tablets and also lower your chance for bleeding problems, you must:

- **Take your regular blood test to check for your response to Jantoven<sup>®</sup> 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 Jantoven<sup>®</sup> 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

- **Many other medicines, including prescription and non-prescription medicines, vitamins and herbal supplements can interact with Jantoven<sup>®</sup> Tablets and:**

- affect the dose you need, or
- increase Jantoven<sup>®</sup> Tablets side effects.

**Tell your healthcare provider about all the medicines you take. Do not stop medicines or take anything new unless you have talked to your healthcare provider. Keep a list of your medicines with you at all times to show your healthcare provider and pharmacist.**

- Do not take other medicines that contain warfarin. **Warfarin is the active ingredient in Jantoven<sup>®</sup> Tablets.**

- **Some foods can interact with Jantoven<sup>®</sup> Tablets and affect your treatment and dose.**

- **Eat a normal, balanced diet.** Talk to your doctor before you make any diet changes. **Do not eat large amounts of leafy green vegetables.** Leafy green vegetables contain Vitamin K. Certain vegetable oils also contain large amounts of Vitamin K. Too much Vitamin K can lower the effect of Jantoven<sup>®</sup> Tablets.
- **Avoid drinking cranberry juice or eating cranberry products.**
- **Avoid drinking alcohol.**

- **Always tell all of your healthcare providers that you take Jantoven<sup>®</sup> Tablets.**

- **Wear or carry information that you take Jantoven<sup>®</sup> Tablets.**

## What are Jantoven<sup>®</sup> Tablets?

Jantoven<sup>®</sup> Tablets are an anticoagulant medicine. They are used to lower the chance of blood clots forming in your body. Blood clots can cause a stroke, heart attack, or other serious conditions such as blood clots in the legs or lungs.

## Who should not take Jantoven<sup>®</sup> Tablets?

### Do not take Jantoven<sup>®</sup> Tablets if:

- **your chance of having bleeding problems is higher than the possible benefit of treatment.** Your healthcare provider will decide if Jantoven<sup>®</sup> Tablets are right for you. Talk to your healthcare provider about all of your health conditions.
- **you are pregnant or plan to become pregnant.** Jantoven<sup>®</sup> Tablets can cause death or birth defects to an unborn baby. Use effective birth control if you can get pregnant.
- **you are allergic to warfarin or to anything else in Jantoven<sup>®</sup> Tablets.**

## What should I tell my healthcare provider before starting Jantoven<sup>®</sup> Tablets?

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

- **have bleeding problems**
- **fall often**
- **have liver or kidney problems**
- **have high blood pressure**
- **have a heart problem called congestive heart failure**

- **have diabetes**

- **drink alcohol or have problems with alcohol abuse.** Alcohol can affect your Jantoven<sup>®</sup> Tablets dose and should be avoided.

- **are pregnant or planning to become pregnant.** See “Who should not take Jantoven<sup>®</sup> Tablets?”

- **are breastfeeding.** Jantoven<sup>®</sup> Tablets may increase bleeding in your baby. Talk to your doctor about the best way to feed your baby. If you choose to breastfeed while taking Jantoven<sup>®</sup> Tablets, both you and your baby should be carefully monitored for bleeding problems.

**Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.** See “What is the most important information I should know about Jantoven<sup>®</sup> Tablets?”

## How should I take Jantoven<sup>®</sup> Tablets?

- **Take Jantoven<sup>®</sup> Tablets exactly as prescribed.** Your healthcare provider will adjust your dose from time to time depending on your response to Jantoven<sup>®</sup> Tablets.
- **You must have regular blood tests and visits with your healthcare provider to monitor your condition.**
- **Take Jantoven<sup>®</sup> Tablets at the same time every day.** You can take Jantoven<sup>®</sup> Tablets either with food or on an empty stomach.
- **If you miss a dose of Jantoven<sup>®</sup> Tablets, call your healthcare provider.** Take the dose as soon as possible on the same day. Do not take a double dose of Jantoven<sup>®</sup> Tablets the next day to make up for a missed dose.
- **Call your healthcare provider right away if you take too many Jantoven<sup>®</sup> Tablets.**
- **Call your healthcare provider if you are sick with diarrhea, an infection, or have a fever.**
- **Tell your healthcare provider about any planned surgeries, medical or dental procedures.** Your Jantoven<sup>®</sup> Tablets may have to be stopped for a short time or you may need your dose adjusted.
- **Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head.** Your healthcare provider may need to check you.

## What should I avoid while taking Jantoven<sup>®</sup> Tablets?

- Do not start, stop, or change any medicine without talking with your healthcare provider.
- Do not make changes in your diet, such as eating large amounts of green, leafy vegetables.
- Do not change your weight by dieting, without first checking with your healthcare provider.
- Avoid drinking alcohol.
- Do not do any activity or sport that may cause a serious injury.

## What are the possible side effects of Jantoven<sup>®</sup> Tablets?

- Jantoven<sup>®</sup> Tablets are very important for your health, but it can cause serious and life-threatening bleeding problems. See “What is the most important information I should know about Jantoven<sup>®</sup> Tablets?”

- **Serious side effects of Jantoven<sup>®</sup> Tablets also include:**

- **death of skin tissue (skin necrosis or gangrene).** This can happen soon after starting Jantoven<sup>®</sup> Tablets. It happens because blood clots form and block blood flow to an area of your body. Call your healthcare provider right away if you have pain, color, or temperature change to any area

of your body. You may need medical care right away to prevent death or loss (amputation) of your affected body part.

- **“purple toes syndrome.”** Call your healthcare provider right away if you have pain in your toes and they look purple in color or dark in color.

**Other side effects with Jantoven® Tablets include** allergic reactions, liver problems, low blood pressure, swelling, low red blood cells, paleness, fever, and rash. Call your healthcare provider if you have any side effect that bothers you.

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

#### **How should I store Jantoven® Tablets?**

- Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from light and moisture. Dispense in a tight, light-resistant container with a child-resistant closure.
- **Keep Jantoven® Tablets and all medicines out of the reach of children.**

#### **General Information about Jantoven® Tablets**

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use Jantoven® Tablets for a condition for which it was not prescribed. Do not give Jantoven® Tablets to other people, even if they have the same condition. It may harm them.



This Medication Guide summarizes the most important information about Jantoven® Tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Jantoven® Tablets that was written for healthcare professionals.



This Medication Guide may have been revised after this copy was produced. For more information and the most current Medication Guide, please visit [www.jantoven.com](http://www.jantoven.com) or [www.upsheer-smith.com](http://www.upsheer-smith.com) or call our professional services department toll-free at 1-800-654-2299.

#### **Rx only**

Jantoven® Tablets are manufactured by  
UPSHER-SMITH LABORATORIES, INC.  
Minneapolis, MN 55447

This Medication Guide has been approved by the U.S. Food and Drug Administration.

JAPI05

Revised 0807