

Revised: December 2011 (19th version)

Standard Commodity Classification No. of Japan
873332

Oral anticoagulant
- Warfarin potassium tablets, JP -

Warfarin Tablets 0.5mg
Warfarin Tablets 1mg
Warfarin Tablets 5mg

Prescription drug

Storage
WARFARIN should be stored at room temperature. The bottle package of WARFARIN should be protected from light after opening cap. (The content of tablets may be decreased, and the color of tablets may be changed by light. In addition, a colored film is used for press-through packages.)

Expiration date
WARFARIN should be used before the expiration date indicated on the package or label.

	Tablets 0.5mg	Tablets 1mg	Tablets 5mg
Approval No.	21600AMZ00224000	15700AMZ00805000	15700AMZ00806000
Date of listing in the NHI reimbursement price	Feb 2004	Feb 1978	Feb 1978
Date of initial marketing in Japan	May 2004	May 1962	Dec 1976
Date of latest reevaluation	—	Aug 1980	

Caution : Use only as directed by a physician.

WARNINGS

It has been reported that the effect of WARFARIN may be enhanced to cause hemorrhage with an occasionally fatal outcome, in patients taking WARFARIN concomitantly with capecitabine.

Patients taking WARFARIN concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters and take appropriate measures as needed.[See “Drug interactions” section.]

CONTRAINDICATIONS (WARFARIN is contraindicated in the following patients.)

- Patients with hemorrhage (due to thrombocytopenic purpura, angioathic bleeding tendency, hemophilia/ other blood coagulation disorders, menstruation, surgery, peptic ulcer, urinary tract hemorrhage, hemoptysis, hemorrhage from genitals immediately after abortion, premature birth or labor, suspected intracranial hemorrhage, etc.)
[WARFARIN may potentiate hemorrhage due to its mechanism of action, and can have fatal consequences.]
- Patients with hemorrhagic tendency (due to visceral tumor, gastrointestinal diverticulitis, colitis, subacute bacterial endocarditis, severe hypertension, severe diabetes mellitus, etc.)
[WARFARIN may cause injured vessels and organs to bleed in the same way as for patients with hemorrhage.]
- Patients with serious hepatic or renal function disorders [Since WARFARIN inhibits hepatic synthesis of vitamin K-dependent coagulation factors, hemorrhage may occur. Delayed metabolism and excretion of WARFARIN may also result in hemorrhage.]

- Patients who have had recent central nervous system surgery or recent trauma.
[WARFARIN may promote hemorrhage which can be fatal consequences.]
- Patients with a history of hypersensitivity to WARFARIN or any of its ingredients.
- Pregnant women or women suspected of being pregnant [See “Important Precautions” and “Use during Pregnancy, Delivery or Lactation” section.]
- Patients on vitamin K₂ (menatetrenone) preparation for treatment of osteoporosis.
[See “Drug Interactions” section]

DESCRIPTION**1. Composition****Tablets 0.5 mg:**

Each light yellow plain, scored tablet contains 0.5 mg of warfarin potassium.

It also contains yellow ferric oxide, microcrystalline cellulose, magnesium stearate, low substituted hydroxypropylcellulose, lactose hydrate and hydroxypropylcellulose as inactive ingredients.

Tablets 1 mg:

Each white plain, scored tablet contains 1 mg of warfarin potassium.

It also contains microcrystalline cellulose, magnesium stearate, low substituted hydroxypropylcellulose, lactose hydrate and hydroxypropylcellulose as inactive ingredients.

Tablets 5 mg:

Each slightly reddish orange, plain scored tablet contains 5 mg of warfarin potassium.

It also contains FD & C Yellow No. 6 (Sunset Yellow

FCF) aluminum lake, microcrystalline cellulose, magnesium stearate, low substituted hydroxypropylcellulose, lactose hydrate and hydroxypropylcellulose.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
WARFARIN Tablets 0.5 mg	Plain tablets				Light yellow, scored
	⊘255	Diameter (mm) 7.6	Weight (mg) 144	Thickness (mm) 2.8	
WARFARIN Tablets 1 mg	Plain tablets				White, scored
	⊘256	Diameter (mm) 8.1	Weight (mg) 190	Thickness (mm) 3.1	
WARFARIN Tablets 5 mg	Plain tablets				Slightly reddish orange, scored
	⊘257	Diameter (mm) 8.6	Weight (mg) 210	Thickness (mm) 3.0	

INDICATIONS

Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, slowly progressing cerebral thrombosis, etc.)

DOSAGE AND ADMINISTRATION

WARFARIN, whose dosage is selected based on blood coagulation test (measurement of prothrombin time and Thrombotest) values, should be used with thorough hemorrhage control. The initial dose is administered orally as a once-daily dose and then adjusted to achieve the target therapeutic range based on blood coagulation test values over several days and thereby determine the maintenance dose.

There are marked individual variations in sensitivity to warfarin and even in the same patient, varying degrees of sensitivity may be observed. Blood coagulation tests should therefore be performed periodically, with the maintenance dose adjusted as necessary.

In order to accelerate the anticoagulant effect, consider coadministering heparin etc. with the first dose of warfarin.

The initial adult dosage is normally 1 to 5 mg of warfarin potassium once daily.

Maintenance doses in pediatric use are shown below.

<12 months: 0.16 mg/kg/day

1 year old ≤ <15 years old: 0.04 to 0.10 mg/kg/day

<Precautions>

- The dose should be determined based on blood coagulation tests (measurement of prothrombin time or Thrombotest), and should be used with through coagulation control so that no deviations from the therapeutic range occur.
- INR (International normalized ratio) is used usually as a notation of prothrombin time or thrombotest values besides activity (%). When using INR for representation of the results of above tests, it is recommended to refer the guidelines issued by medical society of Japan or other countries,

and to consider the patient's age, disease, and concomitant drugs for decision of the therapeutic range.

- The adult maintenance dose is commonly about 1 to 5 mg once daily.

PRECAUTIONS

1. Careful Administration (WARFARIN should be administered with care in the following patients.)

- Patients with hepatitis, diarrhea, malabsorption of fat, chronic alcoholism, congestive heart failure, sepsis, prolonged hypotension, and neonates with vitamin K deficiency.
[The effect of WARFARIN may be enhanced.]
- Patients receiving vitamin K
[The effect of WARFARIN may be diminished.]
- Patients with malignant tumors
[Malignant tumors may enhance coagulation]
- Postpartum puerperants
[Such patients have a tendency to bleed and hemorrhage may be profuse.]
- Patients with hyperthyroidism or hypothyroidism
[These types of thyroid function disorder may be normalized as a result of changes in pathology or therapy being given. This may affect coagulation levels so that the effect of WARFARIN may appear to be diminished or potentiated.]
- Newborn neonates
[See 'Important Precautions' section and 'Pediatric use' section]

2. Important Precautions

- It has been reported that the effect of WARFARIN may be enhanced to cause serious hemorrhage when coadministered with drugs listed in precautions for coadministration. In addition, care should be taken to ensure that the effect of WARFARIN is not enhanced by the dosage, by keeping it in an appropriate range for treatment. Adequate care should also be taken to ensure that the effect of WARFARIN is not diminished.
- Since the abrupt discontinuation of WARFARIN may cause the formation of thrombi, the dose should be tapered off gradually.
- When the anticoagulant effect of WARFARIN needs to be reduced rapidly due to adverse reactions such as hemorrhage, it should be discontinued. In this case, administration of a vitamin K preparation may be required. Serious hemorrhagic events such as cerebral hemorrhage may occur. In the event of such hemorrhage, appropriate measures such as infusion of fresh frozen plasma should be considered. Adequate precautions should be taken against the recurrence of thrombi.
- WARFARIN is not effective in patients taking vitamin K preparations. If treatment with WARFARIN is necessary for these patients, they should not take vitamin K preparations if there is no therapeutic intent for hemostasis.
- WARFARIN should not be administered to pregnant women or women suspected of being pregnant.

When WARFARIN is administered to women who may be pregnant, the risks to patients of WARFARIN teratogenicity, bleeding tendency with fatal outcome for the fetus and that of abnormal bleeding for the mother during childbirth should be explained.

[See “Use during Pregnancy, Delivery or Lactation” section.]

- (6) Pediatric use of WARFARIN should be supervised by a doctor with a thorough knowledge of pediatric treatment with anticoagulant agent.
- (7) Since the safety of WARFARIN in newborn neonates has not been established, this product should only be used in newborn neonates if the expected therapeutic benefits outweigh the possible risks of treatment.

sible combinations of WARFARIN with other drugs. When any drug is added or withdrawn during anticoagulant therapy, the patient’s coagulation levels should be carefully monitored. WARFARIN (S type optical isomer) is metabolized mainly by CYP2C9.

(1) Contraindications for coadministration (WARFARIN should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Vitamin K ₂ preparation for treatment of osteoporosis Menatetrenone (GLAKEY)	Effect of WARFARIN is diminished. If patients must use WARFARIN, it should prefer WARFARIN therapy and discontinue administration of vitamin K ₂ preparation for treatment of osteoporosis.	Vitamin K antagonizes the action of biosynthetic inhibitory of vitamin K dependence coagulation factors of WARFARIN.

3. Drug Interactions

Drug interactions have not been investigated with all pos-

(2) Precautions for coadministration

(WARFARIN should be administered with care when coadministered with the following drugs.)

Drug classification	Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk factors
Hypnotic sedatives	Barbiturates and Thiobarbiturates Phenobarbital	The effects of WARFARIN may be diminished. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs induce hepatic enzymes which metabolize WARFARIN.
	Chloral hydrate Triclofos sodium	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The release of WARFARIN from plasma proteins is promoted by the active metabolite of these drugs.
Antiepileptics	Carbamazepine	The effects of WARFARIN may be diminished. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs induce hepatic enzymes which metabolize WARFARIN.
	Primidone		
	Phenytoin	The effects of WARFARIN may be diminished or enhanced. Additionally, WARFARIN may enhance the effects of Phenytoin. When Phenytoin is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability, poisoning symptoms due to Phenytoin, or increase in blood concentration of Phenytoin.	Since this drug induces hepatic drug-metabolizing enzymes, the effect of WARFARIN is diminished. The effects of WARFARIN are enhanced by this drug which promotes the release of WARFARIN from plasma proteins. WARFARIN enhances the effects of this drug through inhibition of hepatic drug-metabolizing enzymes.
	Ethotoin	The effects of WARFARIN may be enhanced. Additionally, WARFARIN may enhance the effects of Ethotoin. When Ethotoin is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability, poisoning symptoms due to Ethotoin, or increase in blood concentration of Ethotoin.	The release of WARFARIN from plasma proteins is promoted by this drug. WARFARIN inhibits the hepatic metabolism of this drug.
Antipyretic-analgesic anti-inflammatory agents	Sodium valproate	The effects of WARFARIN may be enhanced. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	Hepatic biosynthesis of blood coagulation factors is attenuated by this drug. This drug functions as a platelet aggregation inhibitor. The release of WARFARIN from plasma proteins is promoted by this drug.
	Acetaminophen Celecoxib	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known. CYP2C9 (a hepatic enzyme which metabolizes WARFARIN) is inhibited by this drug. WARFARIN promotes gastric hemorrhage, which is an adverse effect of this drug.

Drug classification	Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk factors	
Antipyretic-analgesic anti-inflammatory agents	Tramadol hydrochloride	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.	
	Bucolome		CYP2C9 (a hepatic enzyme which metabolizes WARFARIN) is inhibited by this drug.	
Antipyretic-analgesic anti-inflammatory agents	Meloxicam Lornoxicam	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9 (a hepatic enzyme which metabolizes WARFARIN) is inhibited by these drugs. These drugs function as platelet aggregation inhibitors. WARFARIN promotes gastric hemorrhage, which is an adverse effect of these drugs. The release of WARFARIN from plasma proteins is promoted by these drugs.	
	Aspirin Ibuprofen Indometacin Indometacin farnesil Etodolac Ketoprofen Salicylates Diclofenac sodium Sulindac Tenoxicam Nabumetone Naproxen Piroxicam Flurbiprofen Mefenamic acid Mofezolac Loxoprofen sodium hydrate, etc.		These drugs function as platelet aggregation inhibitors. WARFARIN promotes gastric hemorrhage, which is an adverse effect of these drugs. The release of WARFARIN from plasma proteins is promoted by this drug.	
Psychoneurologic agents	Trazodone hydrochloride	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.	
	Methylphenidate hydrochloride	The effects of WARFARIN may be enhanced.	These drugs inhibit hepatic enzymes which metabolize WARFARIN.	
	Tricyclic antidepressants Amitriptyline hydrochloride, etc.	When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.		
	Paroxetine hydrochloride hydrate		The mechanism is not known.	
	Fluvoxamine maleate		This drug inhibits hepatic enzymes which metabolize WARFARIN.	
	Monoamine oxidase inhibitor		The mechanism is not known.	
Antiarrhythmics	Amiodarone hydrochloride	The effects of WARFARIN may be enhanced. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9 (a hepatic enzyme which metabolizes WARFARIN) is inhibited by these drugs. Hyperthyroidism, occurring as an adverse effect of this drug, enhances the effects of WARFARIN.	
	Propafenone hydrochloride		This drug inhibits hepatic enzymes which metabolize WARFARIN.	
	Quinidine sulfate		The mechanism is not known.	
Antilipemics	Cholestyramine	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	Gastrointestinal absorption of WARFARIN is inhibited by binding with this drug in the intestine. Enterohepatic circulation of WARFARIN is inhibited by this drug.	
	Simvastatin Fluvastatin sodium Rosuvastatin calcium	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.	
	Fibrates	Bezafibrate		This drug enhances affinity for the site of action of WARFARIN.
		Clinofibrate Clofibrate Fenofibrate, etc.		The mechanism is not known.
		Dextran Sulfate Sodium		This drug possesses an anti-coagulation (anti-thrombin) function.
Drugs for peptic ulcer	Omeprazole	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits hepatic enzymes which metabolize WARFARIN.	
	Cimetidine		CYP1A2, CYP2C9, and CYP3A (hepatic enzymes which metabolize WARFARIN) are inhibited by this drug.	

Drug classification	Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk factors	
Antiemetic	Aprepitant	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9 (hepatic enzymes which metabolizes WARFARIN) is induced by this drug.	
Hormones	Adrenocortical steroids Prednisolone, etc.	The effects of WARFARIN may be diminished or enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This kind of drug diminishes the effects of WARFARIN by enhancing the blood coagulation function. WARFARIN promotes gastric hemorrhage, which is an adverse effect of these drugs.	
	Thyroid preparations Levothyroxine sodium hydrate, etc.	Since this kind of drug relieves the thyroid function disorders due to hypothyroidism, a decrease of blood coagulation ability may occur in patients as if the effects of WARFARIN had been enhanced. When this kind of drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This kind of drug promotes the catabolism of vitamin K-dependent blood coagulation factors.	
	Antithyroid preparations Thiamazole, etc.	The effects of WARFARIN may be enhanced. Since this kind of drugs relieves thyroid function disorders due to hyperthyroidism of blood coagulation ability may be enhanced in patients as if the effects of WARFARIN had been diminished. When this kind of drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability depending on the pathological condition.	Hypoprothrombinemia, a side effect of this kind of drug, promotes bleeding tendency. Hypersynthesis and hypermetabolism of blood coagulation factors due to promotion of thyroid function may enhance the effects of WARFARIN. When thyroid function is recovered by this kind of drugs, the effects of WARFARIN, which were previously enhanced, are diminished.	
	Glucagon	The effects of WARFARIN may be enhanced.	The mechanism is not known.	
	Protein anabolic steroids Nandrolone Decanoate, etc.	When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug enhances affinity for the site of action of WARFARIN. This drug promotes the catabolism of vitamin K-dependent blood coagulation factors. It has been reported that this drug enhances blood coagulation ability.	
	Danazol			
Androgen Methyltestosterone, etc.		Either the inhibition of the synthesis of vitamin K-dependent blood coagulation factors or the degradation of these factors is promoted by this kind of drugs.		
Anti-hemorrhoid agents	Tribenocide Tribenocide/Lidocaine	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.	
Vitamin preparations	Vitamin K and vitamin K preparations	Phytonadione (Vitamin K)	The effects of WARFARIN are diminished. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	Vitamin K antagonizes the effects of WARFARIN which inhibits the synthesis of vitamin K-dependent coagulation factors.
		Menatetrenone (Vitamin K)		
		Enteric nutrients Multivitamin preparations for intravenous hyperalimentation, etc.		
Antithrombotic Agents	Anticoagulants	Heparin sodium Heparin calcium	These drugs and WARFARIN enhance the anti-coagulation effect and bleeding tendency inter-dependently. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring and adjustment of the doses of these drugs.	This drug inhibits the action of blood coagulation factors.
		Low-molecular-weight heparin Dalteparin sodium, etc. Heparinoid Danaparoid sodium		This drug inhibits the action of a blood coagulation factor (factor Xa).
		Factor Xa inhibitor Fondaparinux sodium Edoxaban tosilate hydrate		This drug inhibits the action of a blood coagulation factor (factor Xa).
		Anti thrombin agents Argatropan hydrate Dabigatran etexilate methanesulfonate		This drug inhibits the action of a blood coagulation factor (thrombin).
Anti-thrombotic Agents	Antiplatelet aggregation agents	Aspirin	The effects of WARFARIN may be enhanced. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits platelet coagulation. WARFARIN promotes gastric hemorrhage, which is an adverse effect of this drug. The release of WARFARIN from plasma proteins is promoted by this drug.

Drug classification	Drugs		Signs, Symptoms, and Treatment	Mechanism and Risk factors	
Antithrombotic Agents	Antiplatelet aggregation agents	Ethyl icosapentate Ozagrel sodium Clopidogrel sulfate Sarpogrelate Hydrochloride Cilostazol Ticlopidine hydrochloride Beraprost sodium Limaprost alfadex, etc.	These drugs and WARFARIN enhance bleeding tendency interdependently. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring and adjustment of the doses of these drugs.	These drugs inhibit the platelet coagulation reaction.	
		Thrombolytic agents		Urokinase Alteplase Monteplase, etc.	These drugs dissolve fibrin.
	Dried concentrated human active protein C			This drug inhibits the action of a blood coagulation factor (thrombin).	
	Thrombomodilin alfa			This drug inhibits thrombin synthesis via promotion of protein C activity.	
	Batroxobin			This drug dissolves a blood coagulation factor (fibrinogen).	
Antigout agents	Allopurinol		The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits hepatic enzymes which metabolize WARFARIN.	
	Probenecid			Since this drug inhibits renal tubule secretion, urinary excretion of WARFARIN is decreased.	
	Benzbromarone			CYP2C9 (hepatic enzymes which metabolize WARFARIN) is inhibited by this drug.	
Enzymes	Pronase Bromelain		The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs dissolve fibrin.	
Antidiabetic agents	Sulfonylurea antidiabetic agents Glibenclamide Glimepiride Chlorpropamide Tolbutamide, etc.		The effects of WARFARIN may be enhanced. WARFARIN enhances the hypoglycemic effects of these drugs, and it may cause hypoglycemic symptoms. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for excessive effects due to these drugs and variation in blood coagulation ability.	Since these drugs inhibit hepatic drug-metabolizing enzyme, the effect of WARFARIN is enhanced. WARFARIN inhibits hepatic metabolism of these drugs and enhance the effects of them.	
Antirheumatic agents	Auranofin		It has been reported that WARFARIN enhanced the acute toxicity of this drug in an animal study. Therefore, the coadministration of Auranofin and WARFARIN should be carried out with caution.	The mechanism is not known.	
	Leflunomide			CYP2C9 (hepatic enzymes which metabolize WARFARIN) is inhibited by an active metabolite of this drug.	
Antitumor agents	Azathioprine Aercaptopurine		The effects of WARFARIN may be diminished. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability. In addition, it has also been reported that these drugs enhance the effects of WARFARIN.	These drugs induce hepatic enzymes which metabolize WARFARIN. Mechanism for enhancement of WARFARIN's effects is not known.	
	Tamoxifen citrate Toremifene citrate			The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs inhibit hepatic enzymes which metabolize WARFARIN.
	Gefitinib				The mechanism is not known.
	Erlotinib hydrochloride				Increase in INR and gastrointestinal hemorrhage have been reported when this drug is used with WARFARIN. Administration should be carried out with careful monitoring for variation in blood coagulation ability.
Antitumor agents	Flutamide		The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.	
	Fluorouracils and their combinations	Capecitabine		CYP2C9 (hepatic enzymes which metabolize WARFARIN) is inhibited by this drug.	
		Fluorouracil Tegafur, etc.		The mechanism is not known.	
Imatinib mesilate		CYP2C9 (hepatic enzymes which metabolize WARFARIN) is inhibited by this drug.			

Drug classification	Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk factors
Antiallergic agents	Zafirlukast	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9 (hepatic enzymes which metabolize WARFARIN) is inhibited by this drug.
	Tranilast		The mechanism is not known.
	Ozagrel hydrochloride hydrate	This drug and WARFARIN enhance bleeding tendency interdependently. When this drug is used with WARFARIN, administration should be carried out with careful monitoring.	This drug inhibits platelet coagulation.
Antibiotics	Aminoglycosides	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	Vitamin K production is suppressed by bactericidal effects of these drugs on enterobacteria.
	Chloramphenicols		
	Cephems		
	Tetracyclines		
	Penicillins		
Macrolides	Erythromycin Clarithromycin Roxithromycin	These drugs inhibit hepatic enzymes which metabolize WARFARIN.	
	Azithromycin Telithromycin, etc.	The mechanism is not known.	
Antituberculosis agents	Rifampicin	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug induces hepatic enzymes which metabolize WARFARIN.
	Aminosalicylic Acids Calcium paraaminosalicylate hydrate, etc.	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.
	Isoniazid	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits hepatic enzymes which metabolize WARFARIN.
Chemotherapeutics	Quinolone antibacterial agents	Nalidixic acid	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.
		Ofloxacin Ciprofloxacin Norfloxacin Levofloxacin hydrate, etc.	The release of WARFARIN from plasma proteins is promoted by this drug. The mechanism is not known.
	Sulfa drugs and their combinations Sulfamethoxazole/Trimethoprim Salazosulfapyridine, etc.	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs inhibit hepatic enzymes which metabolize WARFARIN.
Antifungal agents	Griseofulvin	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug induces hepatic enzymes which metabolize WARFARIN.
	Azole antifungal agents	Itraconazole Fluconazole Voriconazole Miconazole, etc.	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.
Anti HIV drugs	Nevirapine	The effects of WARFARIN may be modified. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP3A (hepatic enzymes which metabolize WARFARIN) is affected by this drug.
	Saquinavir Saquinavir mesilate Delavirdine Mesilate Fosamprenavir calcium hydrate	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs inhibit hepatic enzymes which metabolize WARFARIN.
	Atazanavir sulfate	The effects of WARFARIN may be modified. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	The mechanism is not known.
	Ritonavir Lopinavir/ Ritonavir	The effects of WARFARIN may be modified. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	
Antiprotozoal agents	Quinine Hydrochloride hydrate	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits hepatic synthesis of blood coagulation factors.
	Metronidazole	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	This drug inhibits hepatic enzymes which metabolize WARFARIN.

Drug classification	Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk factors	
Others	Bosentan hydrate	The effects of WARFARIN may be diminished. When this drug is used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9, CYP3A4 (hepatic enzymes which metabolize WARFARIN) are induced by this drug.	
	NATTO-KIN (<i>Bacillus subtilis natto</i>)-containing formulation		It has been reported that NATTO diminishes the anticoagulant effect of WARFARIN.	
	Interferon	The effects of WARFARIN may be enhanced. When these drugs are used with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	These drugs inhibit hepatic metabolism of WARFARIN.	
	Disulfiram		The mechanism is not known.	
	Ipriflavone			
Food and Drink	Alcohol	Special care is needed when drinking alcohol and taking WARFARIN because the effects of WARFARIN may be diminished or enhanced.	Induction of WARFARIN drug-metabolizing enzymes due to regular alcohol-consumption diminishes the effect of this product. Hepatic hypoactivity attributed to alcohol-consumption enhances the effects of WARFARIN.	
	Foods containing <i>Hypericum perforatum</i> (St. John's Wort)	The effects of WARFARIN may be diminished. When this kind of foods is taken with WARFARIN, administration should be carried out with careful monitoring for variation in blood coagulation ability.	CYP2C9, CYP3A (hepatic enzymes which metabolize WARFARIN) are induced by this kind of foods.	
	Foods containing vitamin K	NATTO (Fermented soybeans) Chlorella AOJIRU (Green juice: a kind of vegetable drink)	Since the effects of WARFARIN may be diminished by these foods, should be told that they must not take them.	Vitamin K in these foods antagonizes WARFARIN's vitamin K dependent inhibitory action on the synthesis of blood coagulation factors.
		Other foods containing vitamin K	Since the effects of WARFARIN may be diminished if patients eat large amounts of such foods rapidly, patients should be thoroughly informed of this risk.	

4. Adverse Reactions (incidence unknown)

(1) Clinically significant adverse reactions

1) Hemorrhage

Hemorrhage from internal organs (cerebral hemorrhage, etc.), mucosal or subcutaneous hemorrhage, etc. may occur. In the event of such hemorrhage, appropriate measures such as reduction in dosage, temporary discontinuation of the medication, administration of vitamin K preparations or infusion of fresh frozen plasma, should be taken. It is advisable to perform blood coagulation tests (Thrombotest, etc.) at the same time.

2) Skin Necrosis

Transient hypercoagulability may occur due to a rapid decrease in protein C activity at first stage of administration. This may give rise to microthrombi, which may lead to skin necrosis. It is advisable to determine protein C activity prior to the administration of WARFARIN.

3) Hepatic function disorders and jaundice

Hepatic function disorders or jaundice with elevation of AST(GOT), ALT(GPT) A1-P or other symptoms may occur. Patients should be carefully monitored, and if such abnormalities are observed, appropriate measures, such as decreasing the dose or temporary discontinuation of the medication, should be taken.

(2) Other adverse reactions

	Incidence unknown
Hypersensitivity ^{note)}	Rash, pruritus, erythema, urticaria, dermatitis and fever
Hepatic	Elevation of AST (GOT) and ALT (GPT)
Gastrointestinal	Nausea/vomiting, and diarrhea
Dermatologic	Alopecia
Other	Antithyroid effect

Note) In the event of such symptoms, treatment should be discontinued.

5. Use in the Elderly

Since WARFARIN has a high binding rate to plasma albumin (see "Pharmacokinetics" section.), the plasma concentration of free drug may become elevated in the elderly who often have low levels of plasma albumin. WARFARIN should be administered with care regarding the dosage used in the elderly.

6. Use during Pregnancy, Delivery or Lactation

(1) WARFARIN should not be administered to pregnant women or women suspected of being pregnant. [WARFARIN is known to cross the placenta and it has been reported that punctate and other types of achondroplasia nervous system abnormalities and bleeding tendency with fatal outcome for fetuses and abnormal bleeding for the mother at childbirth may occur.]

(2) Nursing mothers should discontinue breast feeding during treatment.

[Since WARFARIN is excreted in breast milk, inadvertent hemorrhage may occur in neonates.]

7. Pediatric Use

The safety in newborn neonates has not been established (insufficient clinical experience).

8. Overdosage

Intravenous vitamin K preparations are effective for hemorrhage due to an overdosage of WARFARIN. Such hemorrhage generally abates within several hours of administering a vitamin K preparation. ¹⁾

9. Precautions concerning Use

Caution in handing over drug

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

Precautions for patients

1. Advice to patients

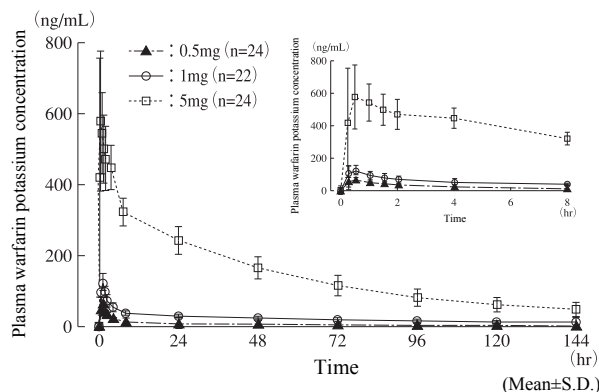
If necessary, patients should be given the following advice in addition to the precautions given in this package insert.

- (1) To always take WARFARIN as directed. (Include directions on what to do in the event of missed dosing.)
 - (2) To consult a doctor regularly and have blood coagulation tests (Thrombotest etc.) without fail.
 - (3) To always consult a doctor prior to surgery or tooth extraction.
 - (4) To refrain from activities that may cause injury.
 - (5) It is advisable to refrain from eating natto (fermented soybeans), chlorella food products and AOJIRU (green juice), as they diminish the anticoagulant effect of WARFARIN.^{2), 3), 4)}
2. When undergoing procedures at other hospitals or departments, the patient should inform the doctor, dentist or pharmacist that they are under treatment with WARFARIN.
 3. Patient medication information and anticoagulant therapy booklets have been prepared for WARFARIN. Patients may obtain this material free of charge.

PHARMACOKINETICS

1. Blood concentration

When WARFARIN was administered orally to healthy adult male volunteers (no indicate CYP2C9*1/*3 and CYP2C9*3/*3 genotype) at a single doses of 0.5mg, 1mg and 5mg, the peak plasma concentrations (C_{max}) were reached 0.5 hr after administration, and the elimination half-life was 55 to 133 hr.



Time course of mean plasma concentration after single oral administration of warfarin potassium

Pharmacokinetic parameters after single oral administration of warfarin potassium

Dose (mg)	Cases	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-144} (ng·hr/mL)	$t_{1/2}$ (hr)
0.5	24	69±17	0.50 (0.25-2.00)	1734±321	133±42
1	22	135±32	0.50 (0.25-1.00)	3442±570	95±27
5	24	685±173	0.50 (0.25-4.00)	21669±3851	55±12

Mean±S.D., t_{max} : median value (minimum value – maximal value)

2. Absorption, distribution, metabolism and excretion

(Data from outside Japan)

Warfarin is well absorbed from the upper gastrointestinal tract in humans after oral administration and 97% of the drug in blood is bound to plasma protein (albumin).⁶⁾

The urinary excretion of unchanged drug accounts for very little of the administered dose, and the main metabolites are warfarin alcohol produced through acetyl group reduction and 6- or 7-hydroxy warfarin.^{7, 8)}

The main subfamily of hepatic drug metabolizing enzymes involved in the metabolism of warfarin is CYP2C9 (S type optical isomer). And it has been reported that CYP1A2 and CYP3A4 (R type optical isomer) are also involved.⁹⁾

CLINICAL STUDIES

Clinical efficacy

(1) Venous thrombosis

WARFARIN was effective in improving vision in patients with retinal venous thrombosis.¹⁰⁾

(Data from outside Japan)

It was also effective in relieving the symptoms of thrombophlebitis, myocardial infarction, coronary failure and pulmonary infarction.¹¹⁾

(2) Coronary occlusion in myocardial infarction

(Data from outside Japan)

A clinical trial was conducted on 92 inpatients with acute myocardial infarction to evaluate the prophylactic effect of warfarin on post-myocardial infarction thrombosis of the fibular vein. In the treated group, in which the Thrombotest value was maintained at 5-15%, venous thrombosis was detected in 3 patients (6.5%) while in the untreated group, 10 patients (22%) were found to have venous thrombosis. The antithrombotic efficacy rate of treated group was significantly higher than in the untreated group ($p < 0.05$).¹²⁾ Also, the following recent randomized clinical trial on long-term anticoagulant therapy has been reported.

In 1,214 patients with myocardial infarction, in the warfarin group total mortality rate decreased by 24% ($p = 0.027$), the recurrent rate decreasing by 34% ($p = 0.0007$) and the incidence rate of cerebrovascular disorders by 55% ($p = 0.0015$) when compared with the placebo group.¹³⁾

(3) Prophylaxis of systemic embolism, including cerebral embolism etc., in non-valvular atrial fibrillation

(Data from outside Japan)

In five large scale randomized clinical trials, the annual incidence rates of embolism in the placebo group were 3.0 - 7.4%, while they were 0.4 - 2.5% for the warfarin group and decreased by 42 - 86% when compared with the placebo group.¹⁴⁻¹⁸⁾

The annual incidence rates of cerebral infarction and systemic embolism were compared for a low dose warfarin plus antiplatelet drug combination dose group and a warfarin ordinary dose group. The annual incidence rates were 7.9% for the combination dose group and 1.9% for the warfarin ordinary dose group.¹⁹⁾

(4) Anticoagulant therapy for post-valve replacement thromboembolism

It has been reported that the annual incidence rate of post-valve replacement thromboembolism in a clinical trial over 1,000 subjects receiving warfarin therapy was 1.4%.²⁰⁾

PHARMACOLOGY

1. Anticoagulant action

The prothrombin time was prolonged by 6 to 18 hrs when warfarin potassium was administered orally to rabbits at a dose of 2 mg/kg. ²¹⁾

2. Antithrombotic action

The carotid arteries of rabbits were ligated to induce the formation of thrombi. Warfarin was administered to these rabbits at doses of 13 to 20 mg/kg/week for 14 to 30 days to evaluate its antithrombotic effect. The weight of thrombi was reduced significantly in the rabbits in which prothrombin activity was depressed to below 15%. ²²⁾

3. Mechanism of action

Warfarin exhibits anticoagulant and antithrombotic effects by antagonizing the action of vitamin K and inhibiting the biosynthesis of vitamin K-dependent coagulation factors (prothrombin, VII, IX and X) in the liver.

PIVKA (Protein induced by Vitamin K absence or antagonist: prothrombin precursor) released into blood after the administration of warfarin exhibits anticoagulant and antithrombotic effects. ²³⁾

PHYSICOCHEMISTRY

Nonproprietary name: Warfarin Potassium (JAN)
Warfarin (INN)

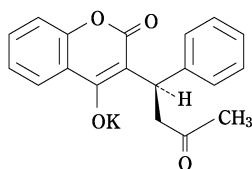
Chemical name:

Monopotassium (*IRS*)-2-oxo-3-(3-oxo-1-phenylbutyl)chromen-4-olate

Molecular formula: C₁₉H₁₅KO₄

Molecular weight: 346.42

Structural formula:



And enantiomer

Description:

Warfarin potassium occurs as a white, crystalline powder. It is very soluble in water and freely soluble in ethanol (95). It dissolves in sodium hydroxide. The pH of an aqueous solution (1 in 100) is 7.2 to 8.3. It is turned light yellow by light. An aqueous solution (1 in 10) shows no optical rotation.

PRECAUTIONS FOR HANDLING

A bister or tango splotch may appear on WARFARIN tablets 0.5 mg and 5 mg tablets due to the dye contained in them.

PACKAGING

Warfarin Potassium Tablets, JP

WARFARIN Tablets 0.5mg:

Boxes of 100 and 1,000 in press-through packages, and bottles of 100 and 500

WARFARIN Tablets 1 mg:

Boxes of 100 and 1,000 in press-through packages, and bottles of 100 and 500

WARFARIN Tablets 5 mg:

Bottles of 100

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Eisai Co., Ltd.

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