Coumadin (warfarin sodium) - Drug Summary

Bristol-Myers Squibb

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Coumadin
(warfarin sodium)

BOXED WARNING

May cause major or fatal bleeding; monitor INR regularly. Drugs, dietary changes, and other factors affect INR levels achieved with therapy. Instruct patients about prevention measures to minimize risk of bleeding and to report signs/symptoms of bleeding.

View FDA-Approved Full Prescribing Information for Coumadin

COMMON BRAND NAMES

Jantoven, Coumadin

THERAPEUTIC CLASS

Vitamin K-dependent coagulation factor inhibitor

DEA CLASS

RX

ADULT DOSAGE & INDICATIONS

Venous Thromboembolism

Including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):
Target INR: 2.5 (INR Range, 2-3) for all treatment durations

Duration of Therapy:
DVT/PE Secondary to Transient Risk Factor: 3 months
Unprovoked DVT/PE: At least 3 months; evaluate risk-benefit ratio of long-term treatment after 3 months of therapy
2 Episodes of Unprovoked DVT/PE: Long-term treatment recommended

Nonvalvular Atrial Fibrillation

Target INR: 2.5 (INR Range, 2-3)

Duration of Therapy:
Persistent/Paroxysmal A-Fib and High Risk of Stroke: Long-term treatment recommended
Persistent/Paroxysmal A-Fib and Intermediate Risk of Ischemic Stroke: Long-term treatment recommended
A-Fib and Mitral Stenosis: Long-term treatment recommended
A-Fib and Prosthetic Heart Valves: Long-term treatment recommended; target INR may be increased and aspirin added depending on valve type and position, and on patient factors

Mechanical/Bioprosthetic Heart Valves

Bileaflet Mechanical Valve/Medtronic Hall Tilting Disk Valve in the Aortic Position in Sinus Rhythm and w/o Left Atrial Enlargement:
Target INR: 2.5 (INR Range, 2-3)

Tilting Disk Valves and Bileaflet Mechanical Valves in the Mitral Position:
Target INR: 3 (INR Range, 2.5-3.5)

Caged Ball or Caged Disk Valves:
Target INR: 3 (INR Range, 2.5-3.5)

Bioprosthetic Valve in the Mitral Position:

Target INR: 2.5 (INR Range, 2-3) for the first 3 months after valve insertion. If additional risk factors for thromboembolism present, target INR 2.5 (INR Range, 2-3)

Post-Myocardial Infarction

High Risk Patients w/ MI:
Treat w/ combined moderate-intensity (INR Range, 2.0-3.0) warfarin plus low-dose aspirin (≤100 mg/day) for at least 3 months after MI

Recurrent Systemic Embolism

Unknown Etiology:
Use a moderate dose regimen (INR Range, 2-3)

Dosing Based on Genotype Consideration

Expected Maint Daily Doses Based on CYP2C9 and VKORC1 Genotypes:
VKORC1-GG:
CYP2C9 *1/*1: 5-7mg
CYP2C9 *1/*2: 5-7mg
CYP2C9 *1/*3: 3-4mg
CYP2C9 *2/*2: 3-4mg
CYP2C9 *2/*3: 3-4mg
CYP2C9 *3/*3: 0.5-2mg

VKORC1-AG:
CYP2C9 *1/*1: 5-7mg
CYP2C9 *1/*2: 3-4mg
CYP2C9 *1/*3: 3-4mg
CYP2C9 *2/*2: 3-4mg
CYP2C9 *2/*3: 0.5-2mg
CYP2C9 *3/*3: 0.5-2mg

VKORC1-AA:
CYP2C9 *1/*1: 3-4mg
CYP2C9 *1/*2: 3-4mg
CYP2C9 *1/*3: 0.5-2mg
CYP2C9 *2/*2: 0.5-2mg
CYP2C9 *2/*3: 0.5-2mg
CYP2C9 *3/*3: 0.5-2mg

CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3:
May require more prolonged time (>2-4 weeks) to achieve max INR effect

If CYP2C9 and VKORC1 Genotypes are Unknown:
Initial: 2-5mg qd
Maint: 2-10mg qd

Other Indications

Mitral Stenosis/Valvular Disease Associated w/ A-Fib:
Use a moderate dose regimen (INR Range, 2-3)

Conversions

From Heparin:
Conversion may begin concomitantly w/ heparin therapy or may be delayed 3-6 days
Continue full dose heparin therapy and overlap warfarin therapy for 4-5 days; D/C heparin once warfarin has produced the desired therapeutic response as determined by INR

Patients receiving both heparin and warfarin should have INR monitoring at least:
5 hrs after the last IV bolus heparin dose, or
4 hrs after cessation of continuous IV heparin infusion, or
24 hrs after the last SQ heparin inj

Warfarin may increase the aPTT test, even in the absence of heparin; severe elevation (>50 sec) in aPTT w/ INR in desired range has been identified as an indication of increased risk of postoperative hemorrhage

From Other Anticoagulants:
Consult the labeling of other anticoagulants for conversion instructions

DOSING CONSIDERATIONS

Elderly
Elderly/Debilitated: Consider lower initial and maint doses

Other Important Considerations
Asian Patients: Consider lower initial and maint doses
Treatment During Dentistry or Surgery: Some procedures may necessitate an interruption or change in dose

ADMINISTRATION

(Coumadin, Jantoven) Oral or (Coumadin) IV route

Coumadin
IV dose is the same as oral dose
IV:
Reconstitute vial w/ 2.7mL of sterile water for inj; resulting yield is 2.5mL of a 2mg/mL sol
After reconstitution, administer as a slow bolus inj into a peripheral vein over 1-2 min

HOW SUPPLIED

Inj: (Coumadin) 5mg; Tab: (Coumadin, Jantoven) 1mg*, 2mg*, 2.5mg*, 3mg*, 4mg*, 5mg*, 6mg*, 7.5mg*, 10mg*
*scored

CONTRAINDICATIONS

Pregnancy, except in pregnant women with mechanical heart valves, who are at high risk of thromboembolism. Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of the CNS, eye, or traumatic surgery resulting in large open surfaces. Bleeding tendencies associated with active ulceration or overt bleeding of GI/genitourinary/respiratory tract, CNS hemorrhage, cerebral aneurysms, dissecting aorta, pericarditis and pericardial effusions, or bacterial endocarditis. Threatened abortion, eclampsia, and preeclampsia. Unsupervised patients with conditions associated with potential high level of noncompliance. Spinal puncture and other diagnostic/therapeutic procedures with potential for uncontrollable bleeding. Major regional, lumbar block anesthesia. Malignant HTN.

WARNINGS/PRECAUTIONS

Has no direct effect on established thrombus, nor does it reverse ischemic tissue damage. Some dental/surgical procedures may need interruption or change in the dose; determine INR immediately prior to procedure. Has a narrow therapeutic range (index) and its action may be affected by endogenous factors, other drugs, and dietary vitamin K; perform periodic INR monitoring. Risk of necrosis and/or gangrene of skin and other tissues; d/c if necrosis occurs and consider alternative therapy. May enhance the release of atheromatous plaque emboli, and systemic atheroemboli and cholesterol microemboli may occur. D/C if distinct syndrome resulting from microemboli to the feet ("purple toes syndrome") occurs. Do not use as initial therapy with heparin-induced thrombocytopenia (HIT) and with heparin-induced thrombocytopenia with thrombosis syndrome (HITTS); limb ischemia, necrosis, and gangrene reported when heparin was discontinued and warfarin started or continued. Can cause fetal harm in pregnant women. Increased risks of therapy in patients with hepatic impairment, infectious diseases/disturbances of intestinal flora, indwelling catheter, severe/moderate HTN, deficiency in protein C-mediated anticoagulant response, polycythemia vera, vasculitis, diabetes, and those undergoing eye surgery. Caution in elderly and hepatic impairment.

ADVERSE REACTIONS

Hemorrhage, necrosis of the skin and other tissues, systemic atheroemboli, cholesterol microemboli, hypersensitivity/allergic reactions, vasculitis, hepatitis, elevated liver enzymes, N/V, diarrhea, rash, dermatitis, tracheal/tracheobronchial calcifications, chills.

DRUG INTERACTIONS

May increase effect (increase INR) with CYP2C9, 1A2, and/or 3A4 inhibitors. May decrease effect (decrease INR) with CYP2C9, 1A2, and/or 3A4 inducers. Increased risk of bleeding with anticoagulants (argatroban, dabigatran, bivalirudin, desirudin, heparin, lepirudin), antiplatelet agents (ASA, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine), NSAIDs (celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac), serotonin reuptake inhibitors (eg, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone). Changes in INR reported with antibiotics or antifungals; closely monitor INR when starting or stopping any antibiotics or antifungals. Use caution with botanical (herbal) products. May potentiate anticoagulant effects with some botanicals (eg, garlic, *Ginkgo biloba*). May decrease effects with some botanicals (eg, coenzyme Q10, St. John's wort, ginseng). Some botanicals and foods can interact through CYP450 interactions (eg, *echinacea*, grapefruit juice, ginkgo, goldenseal, St. John's wort). Cholestatic hepatitis has been associated with coadministration of warfarin and ticlopidine.

PREGNANCY AND LACTATION

Category D (with mechanical heart valves) or Category X (for other pregnant populations), caution in nursing.

MECHANISM OF ACTION

Vitamin K-dependent coagulation factor inhibitor; thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide.

PHARMACOKINETICS

Absorption: (PO) Complete; T_{max}=4 hrs. **Distribution:** V_d=0.14L/kg; plasma protein binding (99%); crosses placenta. **Metabolism:** Hepatic via CYP2C9, 2C19, 2C8, 2C18, 1A2, 3A4; hydroxylation (major), reduction. **Elimination:** Urine (≤92%, metabolites); $T_{1/2}$=1 week.

ASSESSMENT

Assess for risk factors for bleeding (eg, age ≥65 yrs, history of highly variable INR, GI bleeding, HTN, cerebrovascular disease, malignancy, anemia, trauma, renal impairment, certain genetic factors), factors affecting INR (eg, diarrhea, hepatic disorders, poor nutritional state, steatorrhea, vitamin K deficiency, increased vitamin K intake, hereditary warfarin resistance), pregnancy/nursing status, other conditions where treatment is contraindicated or cautioned, and drug-drug/drug-disease interactions. Assess INR. Obtain platelet counts in patients with HIT or HITTS.

MONITORING

Monitor for signs/symptoms of bleeding, necrosis/gangrene of skin and other tissues, systemic atheroemboli, cholesterol microemboli, "purple toes syndrome," and other adverse reactions. Perform periodic INR testing.

PATIENT COUNSELING

Instruct to inform physician if patient falls often as this may increase risk for complications. Counsel to maintain strict adherence to dosing regimen. Advise not to start or stop other medications, including salicylates (eg, ASA, topical analgesics), OTC drugs, or herbal medications, except on advice of physician. Instruct to inform physician if pregnancy is suspected (to discuss pregnancy planning) or if considering breastfeeding. Counsel to avoid any activity or sport that may result in traumatic injury. Instruct that regular PT tests and visits to physician are required during therapy. Advise patient to carry ID card stating drug is being taken. Instruct to eat a normal, balanced diet to maintain consistent intake of vitamin K and to avoid drastic changes in diet, such as eating large amounts of leafy, green vegetables. Advise to take ud. Advise to immediately report unusual bleeding or

symptoms or any serious illness, such as severe diarrhea, infection, or fever. Inform that anticoagulant effects may persist for about 2 to 5 days after discontinuation.

STORAGE

Tab: (Coumadin) 15-30°C (59-86°F). (Jantoven) 20-25°C (68-77°F); excursions permitted 15-30°C (59-86°F). Protect from light and moisture. Inj: (Coumadin) 15-30°C (59-86°F). Protect from light. Use reconstituted sol within 4 hrs. Do not refrigerate. Discard any unused sol.

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