

WARFARIN

Class: Vitamin K Antagonist

Indications : Prophylaxis and treatment of thromboembolic disorders (eg, venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement; adjunct to reduce risk of systemic embolism (eg, recurrent MI, stroke) after myocardial infarction. **Unlabeled:** Prevention of recurrent transient ischemic attacks

Available dosage form in the hospital: 3MG TAB, 5MG TAB

Dosage: Note: Labeling identifies genetic factors which may increase patient sensitivity to warfarin. Specifically, genetic variations in the proteins CYP2C9 and VKORC1, responsible for warfarin's primary metabolism and pharmacodynamic activity, respectively, have been identified as predisposing factors associated with decreased dose requirement and increased bleeding risk. Genotyping tests are available, and may provide guidance on initiation of anticoagulant therapy. The American College of Chest Physicians recommends against the use of routine pharmacogenomic testing to guide dosing (Guyatt, 2012). For management of elevated INRs as a result of warfarin therapy, see Additional Information/Pharmacotherapy Pearls for guidance.

-Prevention/treatment of thrombosis/embolism:

-I.V. (administer as a slow bolus injection): 2-5 mg/day

-Oral: Initial dosing must be individualized. Consider the patient (hepatic function, cardiac function, age, nutritional status, concurrent therapy, risk of bleeding) in addition to prior dose response (if available) and the clinical situation. Start 2-5 mg once daily for 2 days **or** for healthy individuals, 10 mg once daily for 2 days; lower doses (eg, 5 mg once daily) recommended for patients with confirmed HIT once platelet recovery has occurred. In patients with acute venous thromboembolism, initiation may begin on the first or second day of low molecular weight heparin or unfractionated heparin therapy. Adjust dose according to INR results; usual maintenance dose ranges from 2-10 mg daily (individual patients may require loading and maintenance doses outside these general guidelines).

Note: Lower starting doses may be required for patients with hepatic impairment, poor nutrition, CHF, elderly, high risk of bleeding, or patients who are debilitated, or those with reduced function genomic variants of the catabolic enzymes CYP2C9 (*2 or *3 alleles) or VKORC1 (-1639 polymorphism); see table. Higher initial doses may be reasonable in selected patients (ie, receiving enzyme-inducing agents and with low risk of bleeding).

| Range ¹ of Expected Therapeutic Maintenance Dose Based on CYP2C9 ² and VKORC1 ³ Genotypes | | | | | | |
|--|--------|--------|----------|----------|----------|----------|
| VKORC1 | CYP2C9 | | | | | |
| <p>Note: Must also take into account other patient related factors when determining initial dose (eg, age, body weight, concomitant medications, comorbidities). The American College of Chest Physicians recommends against the use of routine pharmacogenomic testing to guide dosing (Guyatt, 2012).</p> | | | | | | |
| <p>¹Ranges derived from multiple published clinical studies.</p> | | | | | | |
| <p>²Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 alleles may take up to 4 weeks to achieve maximum INR with a given dose regimen.</p> | | | | | | |
| <p>³VKORC1 -1639G>A (rs 9923231) variant is used in this table; other VKORC1 variants may also be important determinants of dose.</p> | | | | | | |
| | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| GG | 5-7 mg | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | 0.5-2 mg |
| AG | 5-7 mg | 3-4mg | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg |
| AA | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg |

Renal Impairment:

No adjustment required, however, patients with renal failure have an increased risk of bleeding complications. Monitor closely.

Hepatic Impairment:

Monitor effect at usual doses. The response to oral anticoagulants may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis. INR should be closely monitored.

Common side effect: Cardiovascular: Vasculitis. Central nervous system: Signs/symptoms of bleeding (eg, dizziness, fatigue, fever, headache, lethargy, malaise, pain).
 Dermatologic: Alopecia, bullous eruptions, dermatitis, rash, pruritus, urticaria. Gastrointestinal: Abdominal pain, diarrhea, flatulence, gastrointestinal bleeding, nausea, taste disturbance, vomiting.
 Genitourinary: Hematuria. Hematologic: Anemia, retroperitoneal hematoma, unrecognized bleeding sites (eg, colon cancer) may be uncovered by anticoagulation
 Hepatic: Hepatitis (including cholestatic hepatitis), transaminases increased
 Neuromuscular & skeletal: Osteoporosis (potential association with long-term use), paralysis, paresthesia, weakness
 Respiratory: Respiratory tract bleeding, tracheobronchial calcification

Pregnancy Risk Factor: D (women with mechanical heart valves)/X (other indications)