Formulary decision guide: 
Warfarin sodium 1 mg/1 ml oral suspension

Drug name

Warfarin sodium 1 mg/1 ml oral suspension

Indication

Warfarin oral suspension is indicated for prophylaxis:¹
• of systemic embolism in patients with rheumatic heart disease and atrial fibrillation
• after insertion of prosthetic heart valves
• of venous thrombosis and pulmonary embolism and for use in the treatment of these conditions to prevent their extension.

Dosage

• A baseline coagulation screen and liver function tests should be performed before initiating warfarin therapy¹
• Typical induction dose is 10 mg daily for 2 days but this should be tailored to individual requirements
• Daily maintenance dose is usually 3 to 9 mg taken at the same time each day. The exact maintenance dose depends on the prothrombin time, usually reported as the INR (international normalised ratio), or other appropriate coagulation test
• Warfarin suspension 1 mg/1 ml comes with an oral dosing syringe to facilitate easy dose titration
• Please refer to the summary of product characteristics¹ available at www.medicines.org.uk/emc for use in specific patients.

Mode of action

Warfarin is:¹
• an antithrombotic agent (vitamin K antagonist)
• a synthetic anticoagulant of the coumarin series. It acts by inhibiting the formation of active clotting factors II, VII, IX, and X.

NICE recommendation

• In patients with permanent atrial fibrillation who are receiving antithrombotic therapy to prevent strokes and/or thromboembolism, NICE recommends adjusted-dose warfarin as the most effective treatment.²

Quality and outcomes framework

• Achievement of the QOF indicators on ongoing management of atrial fibrillation requires practices to report the percentage of patients on the atrial fibrillation register:³
  – in whom there is a record of a CHADS₂ score of 1 (latest in the preceding 15 months) and who are currently treated with anticoagulation drug therapy or antiplatelet therapy (QOF indicator AF6)
  – whose latest record of a CHADS₂ score is greater than 1 and who are are currently treated with anticoagulation therapy (QOF indicator AF7).

Evidence for use

• Circulatory diseases (such as heart disease and stroke) are the leading cause of death in England and Wales₄
• Almost 60% of patients aged >60 years experience some difficulty in swallowing solid-dose medications⁵
• Dissolving or crushing warfarin tablets may give poor dose uniformity as the ratio of the S and R enantiomers, which have significantly different potencies, may change,⁶ this may result in underdosing or overdosing.

Compliance and cost effectiveness

• Swallowing difficulties might be one factor that adversely affects compliance, particularly in the elderly and stroke patients
• Warfarin prophylaxis prolongs quality-adjusted survival and yields cost savings for non-valvular atrial fibrillation patients with high risk of stroke.⁷

Contraindications

• Contraindications to warfarin are:¹
  – known hypersensitivity to warfarin or any of the ingredients in warfarin suspension
  – haemorrhagic stroke
  – clinically significant bleeding
  – use within 72 hours of surgery with risk of severe bleeding
  – use within 48 hours postpartum
  – pregnancy
  – use with drugs where interactions lead to a significantly increased risk of bleeding
  – any physical condition in which the risk of haemorrhage might be greater than the potential clinical benefits of anticoagulation.
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Precautions and side-effects

- Please refer to the summary of product characteristics available at www.medicines.org.uk/emc/

Key points

- The following patients, who may become non-adherent, benefit from warfarin sodium oral suspension:
  - those aged >60 years who may have difficulty swallowing warfarin tablets or other solid-dose medications
  - those with transient swallowing difficulties, e.g. patients who have had a stroke
- Warfarin suspension 1 mg/1 ml comes with an oral dosing syringe to facilitate easy dose titration.

Abbreviated Prescribing Information: Warfarin Sodium 1mg/1ml Oral Suspension.
Consult Summary of Product Characteristics before prescribing.
Presentation: A white to off white suspension, each 1 ml of suspension contains Warfarin Sodium 1 mg. Therapeutic Indications: Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation. Prophylaxis after insertion of prosthetic heart valves. Prophylaxis of venous thrombosis and pulmonary embolism and for use in the treatment of these conditions to prevent their extension. Posology: Adults: Between 3 mg and 10 mg per day. Contra-indications: Known hypersensitivity to warfarin or to any of the ingredients contained in warfarin suspension. Haemorrhagic stroke. Clinically significant bleeding or use within 72 hours of surgery with risk of severe bleeding. Use within 48 hours postpartum. Warfarin is contraindicated in pregnancy. Drugs where interactions lead to a significantly increased risk of bleeding. Anticoagulation is contraindicated in any physical condition in which the risk of haemorrhage might be greater than the potential clinical benefits of anticoagulation Precautions: Most adverse events reported with warfarin are a result of over-anticoagulation. If this preparation replaces or is replaced by another warfarin product, the patient should be monitored closely in the period immediately following the change. Thrombophilia: Patients with protein C or S deficiency are at risk of developing skin necrosis when starting warfarin treatment. Haemorrhage can indicate an overdose of warfarin has been taken. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. Minor surgical procedures with low risk of bleeding can be performed in general with an INR of <2.5. Where there is a risk of severe bleeding, warfarin should be stopped 3–5 days prior to surgery. Where it is necessary to continue anticoagulation the INR should be reduced to <2.5 and heparin therapy should be started. If surgery is required and warfarin cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K. The timing for re-instating warfarin therapy depends on the risk of post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake. In most cases warfarin need not be stopped before routine dental surgery. Due to a high risk of bleeding, patients with history of peptic ulcers be reviewed regularly. Many drugs and foods interact with warfarin and affect the prothrombin time. Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. The rate of warfarin metabolism depends on thyroid status; patients with hyper- or hypo-thyroidism should be closely monitored on starting warfarin therapy. The following may exaggerate the effect of warfarin, and necessitate a reduction of dosage: loss of weight, acute illness, cessation of smoking. The following may reduce the effect of warfarin, and require the dosage to be increased: weight gain, diarrhoea, vomiting. Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect. Exciptient warnings: The product contains liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not use this medicine. Interactions: Warfarin has a narrow therapeutic range and the product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring. Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding. Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in warfarin users. Cranberry juice, grapefruit juice, liver, broccoli, Brussels sprouts and green leafy vegetables. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet. Laboratory tests: Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test. Pregnancy and lactation: Contraindicated; women of child-bearing age should use effective contraception during treatment. At therapeutic dosages warfarin may be used during breast-feeding. Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to Rosemont Pharmaceuticals Ltd on 0113 244 1400.

References

1. Rosemont Pharmaceuticals Ltd. Warfarin Sodium 1 mg/1 ml oral suspension. Summary of product characteristics April 2012.

Clotidogrel, NSAIAs, Sulfnpyrazone, Thrombin inhibitors such as bivalirudin, dabigatran, ipyramidol, unfractionated heparins and heparin derivatives, low molecular weight heparins, fondaparinux, rivaroxaban, glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab Prostacyclin, Thrombophilia: Patients with protein C or S deficiency are at risk of developing skin necrosis when starting warfarin treatment. Haemorrhage can indicate an overdose of warfarin has been taken. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. Minor surgical procedures with low risk of bleeding can be performed in general with an INR of <2.5. Where there is a risk of severe bleeding, warfarin should be stopped 3–5 days prior to surgery. Where it is necessary to continue anticoagulation the INR should be reduced to <2.5 and heparin therapy should be started. If surgery is required and warfarin cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K. The timing for re-instating warfarin therapy depends on the risk of post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake. In most cases warfarin need not be stopped before routine dental surgery. Due to a high risk of bleeding, patients with history of peptic ulcers be reviewed regularly. Many drugs and foods interact with warfarin and affect the prothrombin time. Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. The rate of warfarin metabolism depends on thyroid status; patients with hyper- or hypo-thyroidism should be closely monitored on starting warfarin therapy. The following may exaggerate the effect of warfarin, and necessitate a reduction of dosage: loss of weight, acute illness, cessation of smoking. The following may reduce the effect of warfarin, and require the dosage to be increased: weight gain, diarrhoea, vomiting. Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect. Exciptient warnings: The product contains liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Interactions: Warfarin has a narrow therapeutic range and the product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring. Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding. Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin. Drugs which should be avoided if possible: