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

Guidelines in practice

Product current status:				
Product proposed status:				
Date of next meeting:				
Decision:	**Yes**		**No**	
Restricted use:				

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 therapy[1]
- 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 characteristics[1] 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 $CHADS_2$ 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 $CHADS_2$ 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 Wales[4]
- Almost 60% of patients aged >60 years experience some difficulty in swallowing solid-dose medications[5]
- 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.

This formulary decision guide was developed from content provided by Rosemont Pharmaceuticals Ltd in a format developed by *Guidelines in Practice*. It has been reviewed by a member of the *Guidelines in Practice* editorial board. At all times editorial control has remained with *Guidelines in Practice*.

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Precautions and side-effects

- Please refer to the summary of product characteristics[1] 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[5]
  - 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.

References

1. Rosemont Pharmaceuticals Ltd. *Warfarin Sodium 1 mg/1 ml oral suspension.* Summary of product characteristics April 2012.
2. National Institute for Health and Clinical Excellence. Atrial fibrillation. Clinical Guideline 36. London: NICE 2006. Available at: guidance.nice.org.uk/cg36
3. British Medical Association. NHS Employers. *Quality and outcomes framework guidance for GMS contract 2012/13*. London: BMA, NHS Employers, 2012. Available at: www.bma.org.uk/employmentandcontracts/independent_contractors/quality_outcomes_framework/qofchanges2012.jsp#.T3rG2u1LKyE
4. Office for National Statistics. *Births and deaths in England and Wales, 2010*. London: ONS, 2011. Available at: www.ons.gov.uk/ons/publications/index.html
5. Strachan I, Greener M. Medication-related swallowing difficulties may be more common than we realise. *Pharmacy in Practice* 2005; **15** (9): 411–414.
6. Jackson M, Lowey A. *Handbook of extemporaneous preparation*. London: Pharmaceutical Press, 2010: 417–423.
7. Gage B, Cardinalli A, Albers G, Owens D. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995; **274** (23): 1839–1845.

Abbreviated Prescribing Information: Warfarin Sodium 1mg/1ml Oral Suspension.
Consult Summary of Product Characteristics before prescribing. **Presentation:** A white to off white suspension, each 1ml of suspension contains Warfarin Sodium 1mg. **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 3mg and 10mg per day. **Contra-indications:** Known hypersensitivity to warfarin or to any of the ingredients contained in warfarin suspension. Haemorrhagic stroke. Clinically significant bleeding. 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. *Excipient 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: Clopidogrel, NSAIDs, Sulfinpyrazone, Thrombin inhibitors such as bivalirudin, dabigatran, ipyridamole, unfractionated heparins and heparin derivatives, low molecular weight heparins, fondaparinux, rivaroxaban, glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab Prostacyclin, SSRI and SNRI antidepressants, other drugs which inhibit haemostasis, clotting or platelet. Low-dose aspirin with warfarin may increase the risk of gastrointestinal bleeding. **Drug interactions:** allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals, omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate, chloral hydrate, chloramphenicol, cimetidine, danazol, dextropropoxyphene, glibenclamide, phenylbutazone, quinidine, stanozolol, thyroxine, triclofos zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin) erythromycin, sulfamethoxazole, metronidazole, barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin, aminogluthethimide, phenazone, corticosteroids, nevirapine, ritonavir, broad spectrum antibiotics, colestyramine and sucralfate glucosamine. **Interactions with herbal products:** St John's Wort. **Alcohol:** Acute ingestion of a large amount of alcohol may inhibit the metabolism of warfarin and increase INR. Conversely, chronic heavy alcohol intake may induce the metabolism of warfarin. **Interactions with food and food supplements:** 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 can be used during breast-feeding. **Effects on ability to drive and use machines:** No specific effect. **Undesirable effects:** Fever, hypersensitivity, cerebral haemorrhage; cerebral subdural haematoma, haemorrhage, haemothorax, epistaxis, gastrointestinal haemorrhage; rectal haemorrhage; haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena, rash; alopecia; purpura; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis, jaundice; hepatic dysfunction, haematuria, unexplained drop in haematocrit; haemoglobin decreased, purple toes. **Overdose:** The benefit of gastric decontamination is uncertain. If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose, consider activated charcoal. In cases of: *life-threatening haemorrhage; non-life threatening haemorrhage; patients on long-term warfarin therapy without major haemorrhage and patients NOT on long-term anticoagulants without major haemorrhage* please refer to the product SPC. The degree of reversal of anticoagulation must be decided on an individual basis. Full reversal with vitamin K may result in prolonged resistance to warfarin, giving rise to the possibility of valve thrombosis and thrombo-embolism in patients with prosthetic heart valves. **Shelf Life and Storage:** 18 months (1 month after opening). Do not store above 25°C. **Legal Category:** POM **Pack Size and NHS Price:** 150ml - £90.00. **Marketing Authorisation Holder:** Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE. **Date of Preparation:** April 2012

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.