

WARFARIN

DRUG PROTOCOL[®]

DOCUMENT SUMMARY/KEY POINTS

- Warfarin inhibits hepatic synthesis of vitamin-K dependent coagulant and anticoagulant factors and is used in the treatment and prophylaxis of thromboembolic complications in specific paediatric populations.
- Contact Haematology for dose, initiating treatment and monitoring treatment.
- This document outlines contraindications to warfarin use, warfarin interactions and principals of safe warfarin use.
- Appendix 1 references guidelines relating to warfarin use and dosing

CHANGE SUMMARY

- Precautions: addition of interactions
- Dose and duration of treatment: changed to principals of safe warfarin use
- Appendix 1: References relating to warfarin guidance

READ ACKNOWLEDGEMENT

- Medical Officers, Pharmacy staff and Haematologists are required to acknowledge the document.

Note: Separate Practice Guidelines may be required to cover all aspects of management.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

Approved by:	CHW Drug Committee	
Date Effective:	1 st August 2018	Review Period: 3 years
Team Leader:	Medication Safety Pharmacist	Area/Dept: Clinical Governance

Introduction / Background

Warfarin inhibits hepatic synthesis of vitamin-K dependent clotting factors II, VII, IX, X and anticoagulant factors protein C and protein S.

Registered Use

- Prophylaxis and treatment of venous thrombosis and pulmonary embolism.
- Prophylaxis and/or treatment of thrombotic complications associated with atrial fibrillation.
- Adjunct in the treatment of coronary occlusion.

Approved Indications

Warfarin is used for medium or long-term anticoagulation to reduce risk of venous or arterial thrombosis.

Specific patient groups most likely to benefit

Patients who may need anticoagulation with warfarin include those with:

1. Venous thromboembolism (VTE)
2. Arterial thrombosis including strokes
3. Heart disease including prosthetic valves, complex congenital heart disease, coronary artery aneurysm, cardiomyopathy

Contraindications

- Clinically significant active bleeding or significant risk of serious bleeding
- Severe hypertension
- Pregnancy

Precautions

Interactions

Warfarin has the potential to interact with numerous medications and alcohol, causing derangements in INRs. The INR should be monitored whenever a drug is added to, or withdrawn from, the patient's treatment regimen. Check for all interactions in established clinical resources such as MIMs or Micromedex or contact pharmacy for further advice.

The following is not an exhaustive list^{1,2}.

- Warfarin effect is potentiated by erythromycin, imidazoles, ciprofloxacin, metronidazole, amiodarone, thyroxine, aspirin and other non-steroidal anti-inflammatory analgesics.
- Warfarin effect is reduced by barbiturates, rifampicin, griseofulvin, carbamazepines and phytomenadione
- Warfarin effects may be reduced or potentiated by phenytoin, corticosteroids or cholestyramine

INRs may also become unstable during inter-current illness such as infections. Diarrhoea can cause the INR to increase quickly, due to the loss of vitamin K generating normal flora in the gut.^{3,4}

Parents should notify the doctor monitoring their child's INR of changes in the child's medications (e.g. new medications or dosage changes) or if the child is unwell with inter-current infections as more frequent monitoring of the INR may be required.

Complications

The most common complications of warfarin relates to degree of anticoagulation:

- Bleeding risk: This is the main adverse event associated with warfarin treatment and occurs when the INR is too high (supra therapeutic). The reported rate of significant bleeding in patients requiring warfarin is less than 1% per year.⁵
- Osteoporosis: As a vitamin K antagonist, warfarin may also inhibit vitamin K-dependent osteocalcin, with potential impact on bone-building and bone mineralization. It is recommended that patients maintain adequate dietary calcium intake and weight-bearing exercises.

Other complications are rare and include:

- Skin necrosis
- Alopecia
- Allergy,
- Tracheobronchial calcification

Principals of dosing and duration of treatment

- Warfarin exhibits inter- and intra-patient variability. Contact Haematology for advice on dosing, treatment initiation and monitoring. During an inpatient admission, it is the responsibility of the primary treating team to develop a warfarin management plan for each patient in consultation with the Haematologist on-call.
- Further information about warfarin dosing and adjustment is available in resources contained in Appendix 1. Warfarin should be given at the same time each day. This is usually 6pm when charted on the MAR.
- Warfarin takes 48-72 hours to produce an anticoagulant effect, with the effect of dose adjustments lagging by a similar amount of time.
- During induction of anticoagulation with warfarin, there is a transient period of increased thrombotic risk due to a disproportionate fall in anticoagulant proteins C and S in comparison to procoagulant clotting factors II, VII, IX and X. Patients switching from unfractionated heparin (UFH) or low molecular weight heparin (LMWH) should continue either heparins until therapeutic INR has been achieved for two consecutive days

Target INR^{7,9}:

The level or adequacy of anticoagulation provided by warfarin is monitored by the INR (*International Normalised Ratio*).

The desired or target INR is determined by the primary treating doctor and is dependent of indication for anticoagulation; for example:

	<i>Target Range</i>
<i>Ischaemic Stroke / Moya Moya</i>	2.0 – 3.0
<i>Deep Vein Thrombosis / Pulmonary Embolism</i>	2.0 - 3.0
<i>Post Fontan Surgery</i>	2.0 – 3.0
<i>Cardiomyopathy</i>	2.0 – 3.0
<i>Pulmonary Hypertension</i>	2.0 – 3.0
<i>Prosthetic Valve</i>	2.5 – 3.5
<i>Recurrent thrombosis despite anticoagulation</i>	3.5 – 4.5

Duration of anticoagulation:

- Duration of treatment is determined by the primary treating doctor.

Authorised Prescribers

All Medical Officers

Administration

Warfarin tablets are available in two brands; Coumadin and Marevan. These brands have **not** been demonstrated to be bioequivalent and should not be used interchangeably. There is an increased therapeutic response with the Coumadin brand of warfarin. The Children's Hospital Westmead and the Sydney Children's Hospital Pharmacy stocks the Coumadin brand.

Mix crushed warfarin with soft foods when administering to infants and young children. Due slow and incomplete dissolution in water or liquids, any undissolved residue may constitute a significant portion of the required dose, particularly when the prescribed dosage may only be 1 – 2 mg.

Infants taking vitamin fortified milk formula can be adequately anticoagulated with warfarin.

Safety and Patient Monitoring

Patients and/or parents should be educated on indications for warfarin, monitoring requirements, potential for interactions and complications. The family should meet with the Haematology registrar for an education session prior to discharge from hospital.

- A Pharmacist should provide Warfarin counselling to all patients during their admission or at discharge.
- Refer to Haematologists for:
 - Frequency of monitoring
 - Medication changes

Patients may attend the Anticoagulation Clinic at CHW, the family GP or paediatrician for outpatient INR monitoring. Monitoring after leaving hospital:

- Arrangements for outpatient INR monitoring should be made prior to the patient's discharge. Confirm with the family GP that s/he would be happy to manage warfarin anticoagulation in a child before referring the patient to the GP for INR monitoring.
- Home INR testing with the CoaguChek XS™ may be appropriate for some patients. Refer to the following policies: [Home INR Testing – Guide for Patients on Long-term Warfarin](#) and [Home INR Testing – Patients on Long-Term Warfarin Treatment – Haematology CHW](#)

Prescribing Warfarin

All inpatient medication at CHW is prescribed through the eMR. This [Quickstart](#) provides a step by step guide on ordering anticoagulants at CHW.

Any special requirements (admission, other medications, tests)

Peri-operative measures

- Contact Haematology

References

1. MIMs online, NSW Health. UBM Medica; Clinical Information Access Program (CIAP). <http://www.ciap.health.nsw.gov.au/>. Australia; Accessed: 15/12/17
2. Micromedex online, Drug Dex Evaluations. Health Communications network; Clinical Information Access Program (CIAP). <http://www.ciap.health.nsw.gov.au/>. Australia; accessed: 15/12/17
3. Hull R, Garcia D, Vazquez S (2017) Biology of warfarin and modulators of INR control In T. W. Post (Ed.), *UptoDate*. Waltham, MA: UptoDate Inc. <http://www.uptodate.com.acs.hcn.com.au> (Accessed on December 15, 2017.)
4. Black JA. Diarrhea, vitamin K, and warfarin (letter). *Lancet* 1994;344:1373.
5. The Royal Childrens Hospital Melbourne. Warfarin guideline for clinicians. [Internet]. Melbourne (VIC). Royal Children's Hospital 2014. [updated 2014; cited 2018 March 05]. Available from: https://www.rch.org.au/haematology/anticoagulation_service/Warfarin_Guidelines_for_Clinicians/
6. Barnes C, Newall F, Cameron F, Wong P, Monagle P. Reduced bone density in children on long-term warfarin. *Pediatr. Res.* 2005; 57: 578–581.
7. Monagle P, Chan A, Goldenberg N, Ichord R, Journeycake J, Nowak-Gottl U, Vesely S. Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based clinical practice guidelines. *Chest.* 2012;141:e737-e801S.
8. Monagle P, Newall F. Anticoagulation in Children. *Thrombosis Research.* 2012;130:124-46
9. Commencement of warfarin therapy in children following the Fontan procedure. Crone E, Hume E, George S, Saliba N, Newall F, Jones S. *Thrombosis Research.* 131(4): 304-307. 2013

10. Bauman M, Black L, Massicotte P et al. Accuracy of the CoaguChek XS for point-of-care international normalized ratio (INR) measurement in children requiring warfarin. *Thromb. Haemost.* 2008; 99: 1097–1103.

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Appendix 1: References relating to warfarin guidance

1. Warfarin in *AMH Children's Dosing Companion* (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2017 July. Available from: <https://childrens.amh.net.au/>
2. Monagle P, Chan A, Goldenberg N, Ichord R, Journeycake J, Nowak-Gottl U, Vesely. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 Feb: 141(2 Suppl). Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22315277><https://www.ncbi.nlm.nih.gov/pubmed/22315277>
3. Warfarin in Meds4Kids Dosing Guide. Available from: <http://webapps.schn.health.nsw.gov.au/meds4kids/browse/W>
4. Warfarin Monograph in Evelina London Paediatric Formulary. Available from: <http://cms.ubqo.com/public/d2595446-ce3c-47ff-9dcc-63167d9f4b80/content/b01e7304-6f90-47d3-abcb-7c835b093de5>
5. The Royal Children's Hospital Melbourne: Warfarin Guidelines for Clinicians Online. Available from: https://www.rch.org.au/haematology/anticoagulation_service/Warfarin_Guidelines_for_Clinicians/