

DRUG GUIDELINE

WARFARIN



SCOPE (Area): FOR USE IN: All ward areas
EXCLUSIONS: Paediatrics (seek Paediatrician advice)
SCOPE (Staff): Medical, Nursing and Pharmacy

BRAND NAMES

Coumadin

Marevan

Note: *Coumadin* and *Marevan* are not interchangeable.

Warfarin is also known as warfarin sodium.

PHARMACOLOGY AND PHARMACOKINETICS

Warfarin inhibits the synthesis of vitamin K dependent clotting factors (II, VII, IX, X) resulting in an anticoagulant effect. Warfarin is completely absorbed after oral administration with peak concentrations obtained within four hours, but distribution into tissue takes 6-12 hours. However, the anticoagulant effect of warfarin is delayed as it only reduces the production of new clotting factors, and any clotting factors already produced and still circulating will exert an effect until they are gradually degraded by the body. As such warfarin takes 5-6 days after initiation to achieve its full effect, and any subsequent dose change will generally take 48-72 hours to become fully apparent. Warfarin also inhibits the synthesis of the antithrombotic factors protein C and protein S, and these are degraded by the body quicker than the vitamin K dependent clotting factors. This can result in a paradoxical hypercoagulable state in the first few days when warfarin is started resulting in skin necrosis. As such patients with an acute thrombotic illness require bridging heparin or enoxaparin for a minimum of 5 days. Approximately 99% of warfarin is bound to plasma proteins, and conditions resulting in low albumin may produce an exaggerated response to warfarin. Elimination is almost entirely by metabolism (the metabolites have minimal anticoagulant activity), with an effective half-life ranging from 20 to 60 hours (mean of about 40 hours).

INDICATIONS

- **Prevention and treatment of venous thromboembolism.**
- **Prevention of thromboembolism in patients with prosthetic heart valves.**
- **Prevention of stroke in patients with previous myocardial infarction and increased embolic risk.**
- **Patients with atrial fibrillation and an increased risk of stroke or systemic embolism.**
- **Anticoagulation prior to cardioversion.**

CONTRAINDICATIONS

- **Severe active bleeding or disease states with an increased risk of severe bleeding** (e.g. severe uncontrolled hypertension, severe hepatic disease, severe thrombocytopenia, active peptic ulcer disease, past history of haemorrhagic stroke (except where cause eliminated), some types of recent surgery).
- **Alcoholism** – with ongoing alcohol intake.
- **Hypersensitivity to warfarin.**

PRECAUTIONS

- **Protein C or protein S deficiency** - increases risk of skin necrosis.
- **Patients with an increased risk of bleeding** (e.g. elderly, frequent falls, severe renal impairment) - assess the risk and benefits carefully for each patient before prescribing warfarin.
- **Dual antiplatelet therapy** - increased risk of bleeding.
- **Compliance with dosing and/or INR monitoring is likely to be poor** - avoid unless administration and blood tests are supervised.
- **Patients living a long distance from the nearest blood collection point** – the likelihood of these patients obtaining blood tests when they are due, and the suitability of warfarin must be assessed.
- **Women of childbearing age** – exclude pregnancy before prescribing, and ensure adequate non-hormonal contraception is arranged if required.
- **Spinal injection or puncture** - seek specialist advice before considering intrathecal or epidural analgesia or anaesthesia, or lumbar puncture (risk of epidural haematoma, which may cause paralysis).
- **Surgery** – the risk of bleeding during surgery increases with the INR. Depending on the indication for warfarin and type of elective surgery (and associated bleeding risk), warfarin may be stopped 4-5 days before surgery. Some patients will require anticoagulation cover pre-operatively and post-operatively. For urgent surgery warfarin reversal may be required. Seek surgical or specialist clinical advice.

PREGNANCY AND BREASTFEEDING

Warfarin is Category D and avoided in pregnancy. Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

- **Many drugs (and complementary medicines) interact with warfarin by increasing or decreasing its anticoagulant effect, or having an additive effect on bleeding. These interactions can result in INR changes ranging from non-significant to life-threatening.**
- **Consult the following drug interaction texts.** Listings are alphabetical, but may be under generic drug name or drug class – check both. Seek Pharmacy advice if required.
 - **Australian Medicines Handbook**
<https://amhonline.amh.net.au.acs.hcn.com.au/?acc=36265>
 - **UpToDate**
<http://www.uptodate.com/contents/search> - select Drug Interactions heading and then type in warfarin.
- **Drugs with an additive effect on bleeding (e.g. antiplatelets, thrombolytics, NSAIDs)** – avoid combination with warfarin or monitor closely. Some patients at high risk of arterial thrombosis may require low dose aspirin (maximum of 150mg/day) as well as warfarin.
- **Known drug interaction increasing or decreasing the anticoagulant effect of warfarin**
 - Substitute a non-interacting drug where possible.
 - Where no substitute exists, check the INR 48-72 hours (or daily if the patient's clinical condition warrants) after commencing or altering the interacting drug to ensure any change in INR is detected. Some drugs will require a reduction of the warfarin dose as they are started (e.g. amiodarone).
- **No known drug interaction** - new drug interactions with warfarin are reported regularly, and the addition of any drug to a warfarin regime has the potential to affect INR.
- **Complementary medicines** – many are known to interact with warfarin (e.g. fish oil, glucosamine, St John's wort). Seek Pharmacy advice.
- **Diet** – vitamin K in food (found particularly in green leafy vegetables) can counteract the effects of warfarin. Patients must be advised to maintain consistency in their diet.

DOSAGE AND ADMINISTRATION

Consider carefully if the benefits of anticoagulation outweigh the bleeding risks for each patient. Discuss these with the patient/carer, including the likely duration of warfarin and the potential risks of stopping treatment without medical advice.

The degree of anticoagulation provided by the same dose of warfarin has great inter-patient variability and is determined by multiple factors (e.g. age, liver function, nutritional status, co-morbidities, other medications, some foods and genetic differences in metabolism). Some patients may have a decreased INR response to warfarin (e.g. acquired or hereditary warfarin resistance, some drugs).

Due to this variability close monitoring of the INR is required to assess the effect of warfarin and tailor dosing to the individual. Patients with highly variable INRs are at a greater risk of bleeding, and will require more frequent INRs and a review of other drugs, compliance and diet.

Check for drug interactions (or contact Pharmacy) when new drugs are to be added to warfarin (see Drug Interaction section). Warfarin dosing used in the *Warfarin Initiation Dosing Table* below will account for potential drug interactions initially, but when interacting drugs are ceased or have dose changes after INR stabilisation more frequent INRs may be required.

Coumadin and *Marevan* brands of warfarin are not interchangeable. Patients new to warfarin are commenced on *Coumadin*, any patient already on *Marevan* is to continue on *Marevan*. Any patient admitted on a mixture of *Coumadin* and *Marevan* should be converted to *Coumadin* and monitored carefully for 5-6 days.

When prescribing warfarin on the drug chart ensure the brand used by the patient is circled, and the target INR and indication filled in. The dose each day must be recorded and signed by the prescriber, together with any INR results. Round all doses to the nearest 0.5 mg. Warfarin is administered once daily at 1600, and INRs are to be taken at 0800-1000 (unless urgent).

Alert the ward Pharmacist or Pharmacy as soon as possible regarding patients commencing warfarin to ensure they can be given a warfarin booklet and counselling.

For treatment of bleeding or excessive INR related to warfarin administration seek senior/specialist advice and refer to Management of Warfarin Toxicity (CPG0120) and Prothrombinex® Administration (CPP0569)

Warfarin Prescribing Guide

When a patient is admitted to hospital and the intent is to treat the patient with warfarin whilst an inpatient, a warfarin prescribing guide will be placed, by nursing staff, with the patient's medication chart. This remains in place throughout their hospital stay. Alternatively wards may choose to leave a warfarin prescribing guide in each end of bed folder.

Laminated prescribing guides will be available in all clinical areas or refer to Appendix Two: Warfarin Prescribing Guide.

PATIENTS COMMENCING WARFARIN

- Perform baseline INR, FBE (platelets), LFT (include albumin) and (if appropriate) a pregnancy test prior to starting warfarin. Abnormal results require specialist clinical advice before proceeding (e.g. Haematologist).
- Patients with an acute thrombotic illness (e.g. PE, DVT) require bridging full anticoagulation (with IV heparin or subcut enoxaparin as appropriate) before commencing warfarin to prevent skin necrosis that can occur with paradoxical hypercoagulability during the first few days of warfarin therapy. Warfarin can however start on the same day as heparin or enoxaparin. **Both drugs need to continue together for a minimum of 5 days AND until the INR is greater than 2 for at least 2 consecutive days.**
- Full bridging anticoagulation may not be required for patients with atrial fibrillation who are not at a high risk of an immediate thrombotic event.
- Determine target INR. INR for most indications is 2 to 3, for mechanical heart valves target INR is 2.5 to 3.5.

Table One provides guidance for **warfarin initiation (target INR 2 to 3)**. Always use clinical judgement when selecting doses and seek specialist clinical advice if required.

Table One: Warfarin Initiation - suggested dosing (with target INR 2 to 3)

Warfarin Initiation Nomogram (target INR 2 to 3)		
Day	INR	Dose
1	less than 1.4	5 mg
2	less than 1.8	5 mg
	1.8 to 2.0	1 mg
	more than 2.0	Withhold
3	less than 2.0	5 mg
	2.0 to 2.5	4 mg
	2.6 to 2.9	3 mg
	3.0 to 3.2	2 mg
	3.3 to 3.5	1 mg
	more than 3.5	Withhold
4	less than 1.6	7 mg
	1.6 to 1.7	6 mg
	1.8 to 1.9	5 mg
	2.0 to 2.3	4 mg
	2.4 to 3.0	3 mg
	3.1 to 3.2	2 mg
	3.3 to 3.5	1 mg
	more than 3.5	Withhold

- Certain patient groups are more likely to be sensitive to warfarin and require lower doses to achieve the target INR. Consider initiating warfarin at lower doses (2-4 mg) for patients with one or more of the following risk factors:
 - Elderly
 - Low body weight
 - Compromised nutrition

- Congestive heart failure
- Abnormal liver function
- Concurrent medicines that increase the anticoagulant effect of warfarin or have an additive effect on bleeding
- High bleeding risk
- INR may be omitted on Day 2 if patient considered low risk of sensitivity to warfarin and bleeding (e.g. absence of above risk factors)
- After Day 4, dose according to *Warfarin MAINTENANCE Dosing* Table below (**Table Two**) for target INR 2 to 3. Always use your clinical judgement when selecting doses and seek specialist clinical advice if required.

Table Two: Warfarin Maintenance - suggested dosing (with target INR 2 to 3)

Warfarin MAINTENANCE Dosing (with target INR 2 to 3)	
INR	DOSAGE ADJUSTMENT*
Less than 2	Increase daily dose by 5 – 20 %
2.1 to 3	No change
3.1 to 3.5	Decrease daily dose by 5 – 15 %
3.6 to 4	Withhold until INR is within therapeutic range; Then decrease daily dose by 10 – 15 %
4.1 to 5	Withhold until INR is within therapeutic range; Then decrease daily dose by 10 – 20 %
INR greater than 5 OR if patient has significant bleeding OR high risk of bleeding	Refer to Management of Warfarin Toxicity (CPG120) and Prothrombinex Administration (CPP0569)
* Dose adjustment may need to be modified in the presence of intercurrent illness. Round dose to the nearest 0.5 mg.	

- Warfarin initiation and maintenance for other target INRs - use clinical judgement, seek specialist clinical advice if unsure.
- Once the INR has been stable in the target INR range for two consecutive days, twice weekly INRs are sufficient unless the clinical status of the patient requires more frequent monitoring.

PATIENTS ADMITTED ALREADY ON WARFARIN

- Check the indication for warfarin (and target INR) and assess need for ongoing therapy.
- Perform INR on admission, adjust warfarin dose (if required) according to *Warfarin MAINTENANCE Dosing (with target INR 2 to 3)*-**Table Two**. Use clinical judgement or seek senior advice for different target INRs.
- If INR is outside target INR range, investigate the reason/s why (e.g. intercurrent illness, drug interaction, non-compliance) as the proposed usual dose adjustment may require modification.
- If stable repeat INR twice weekly unless the clinical status of the patient requires more frequent monitoring. If sufficiently stabilised, long term patients may have less frequent INR monitoring at the discretion of the treating team.
- If unstable repeat daily. Once the INR has been stable in the target INR range for two consecutive days, twice weekly INRs are sufficient unless the clinical status of the patient requires more frequent monitoring.

PATIENTS RECOMMENCING WARFARIN POSTOP

- Restart no higher than the usual maintenance dose for the patient (taking into account drug interactions etc) – DO NOT RE-LOAD.
- Check INR every second day unless other factors necessitate daily INRs.
- Once at target INR, repeat INR the next day. Once the INR has been stable in the target INR range for two consecutive days, twice weekly INRs are sufficient unless the clinical status of the patient requires more frequent monitoring.

PATIENTS DISCHARGED PRESCRIBED WARFARIN (includes patients with warfarin currently withheld)

All patients discharged from hospital using warfarin must:

- Receive written information regarding their current dose and timing of next INR. This is the responsibility of the clinical pharmacist. Where a clinical pharmacist is not on duty the treating team is responsible. Examples of appropriate written information include a warfarin book, medicines list or MR/092.2 Summary Warfarin & Anticoagulation Dosing form.
- Receive a pathology slip to receive their next INR. This is the responsibility of the treating team.
- Have MR/092.2 Summary Warfarin & Anticoagulation Dosing form completed. A copy of this form must be given to the patient/carer for their GP. A copy of the form will be faxed to the GP, when the GP's details are known. This is the responsibility of the clinical pharmacist. If a clinical pharmacist is not on duty the treating team will complete and fax.
- Patients being transferred to a community based programs (e.g. HITH, GITH) will receive written information when being transferred to the community based program and when discharged from the community based program. From hospital this is the responsibility of the clinical pharmacist. From the community based program and/or if a clinical pharmacist is not on duty this is the responsibility of the treating team. When being discharged from the community based program a pathology slip should be supplied and MR/092.2 Summary Warfarin & Anticoagulation Dosing form completed and faxed. This is the responsibility of the treating team.
- Receive counselling from a clinical pharmacist prior to discharge. The clinical pharmacist will sign the warfarin counselling section of the NIMC to highlight this has occurred. Where a clinical pharmacist is not on duty this is the responsibility of the treating team.

Patients being transferred to another hospital do not require written information to be given to the patient regarding dosing information, a pathology slip or MR/092.2 Summary Warfarin & Anticoagulation Dosing form. The appropriate interhospital transfer form should be completed, highlighting the use of a high risk medication and current dosing/INR information.

Patients being transferred to a Residential Aged Care Facility (RACF) do not require written information, but will require a pathology slip and MR/092.2 Summary Warfarin & Anticoagulation Dosing form with a copy given to the and faxed to the GP. Information may be supplied to the patient regarding current dose and next INR if the patient is of a high functioning state.

These responsibilities are summarised in **Table Three: Information Required at Discharge.**

Table Three: Information Required at Discharge

Discharge to:	Home		Nursing Home		Other hospital		To community based program (HITH, GITH)		Community based program to home	
Responsible Person Info Required	Pharm	MO	Pharm	MO	Pharm	MO	Pharm	MO	Pharm	MO
MR/092.2	✓	*	✓	*						✓
Path Slip		✓		✓						✓
Dosing Information	✓	*					✓	*		✓
Verbal Counselling	✓	*					✓	*		✓

*Note: where a clinical pharmacist is not on duty the written information becomes the responsibility of the treating team.

MONITORING (INCLUDING BLOOD TESTS)

- Perform baseline INR, FBE (platelets), LFT (including albumin) and (if appropriate) a pregnancy test prior to starting warfarin.
- Repeat INRs as outlined in Dosage and Administration.
- Monitor for any signs of bleeding (external bruising, abdominal distension/pain, back pain, hypotension and shock, collapse, neurological symptoms, macroscopic haematuria, haemoptysis, epistaxis, GIT blood loss, headache, dyspnoea, stridor, unexplained fall in haemoglobin).
- Monitor for skin necrosis (a rare adverse effect of warfarin, but can occur within a few days of starting warfarin). Stop warfarin if necrosis occurs, and consider heparin.
- Monitor for purple toe discolouration (a rare adverse effect of warfarin, most likely occurring 3-10 weeks after starting warfarin). Stop warfarin if purple toe discolouration occurs, and consider heparin.

NURSING PRACTICE POINTS

- Observe for any signs/symptoms of bleeding (see Monitoring).
- The correct brand of warfarin must be administered as they are not interchangeable.
- Warfarin doses are to be given at 1600. If the dose has not been prescribed by 1600, contact the Prescriber.
- Ensure you know when the next INR is due and that blood is taken between 0800-1000 (unless urgent INR required).
- Ensure if the most recent INR was above the target range that the Prescriber has withheld or lowered the next dose.
- Ensure Pharmacy is contacted to provide warfarin education and a warfarin booklet to the patient. This booklet should be updated with doses and INRs during the patient's admission.
- Warfarin requires an independent double check – see Medication Administration CPP0287
- Where possible, whole bottles of warfarin will be supplied from pharmacy. This includes patients being managed through Community Based Programs (e.g. HITH).
- Indwelling catheters** – monitor for signs of bleeding.
- Intramuscular injection** – avoid where possible. Only administer to the upper extremities, which permits easy access for manual compression, inspection for bleeding and use of pressure bandages.
- Venepuncture or other superficial grazes** - may require the application of a pressure dressing for up to 30 minutes.
- Arterial punctures** – require a minimum of 10 minutes digital compression.

ADVERSE EFFECTS

The most serious risks associated with warfarin are haemorrhage and, less frequently (< 0.1%), skin necrosis. Haemorrhage and necrosis have in some cases been reported to result in death or permanent disability.

Common - bleeding (ranging from mild to severe) in any tissue or organ. The risk of haemorrhage increases as the INR increases.

Rare - skin necrosis (appears to be associated with local thrombosis and usually appears within a few days of initiation with warfarin), systemic cholesterol microembolisation (including purple discolouration of toes which generally occurs between three to ten weeks after the initiation of therapy with warfarin), alopecia, fever, rash, nausea, vomiting, diarrhoea, hepatic dysfunction, vasculitis, oedema, abdominal pain, cold intolerance, taste perversion, dizziness, headache, allergic reactions.

DRUG PRESENTATIONS, LOCATION AND STORAGE

Coumadin®: 1mg, 2mg and 5mg tablets.

Marevan®: 1mg, 3mg and 5mg tablets.

Imprest Locations (at the time of guideline development): Coumadin® - most wards. Marevan® - individual patient supply from Pharmacy only.

Store below 25°C.

RELATED DOCUMENTS

CPG0120	Management of Warfarin Toxicity
DRG0031	Prothrombinex Administration
CPP0287	Medication Administration
CPP0549	High Risk Medications

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