Prescribing guidelines for the management of patients on warfarin in primary care

February 2018

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Date revised: February 2018
Review date: February 2020

Background

Warfarin anticoagulation is widely used for many clinical indications. Warfarin has a narrow therapeutic index and close monitoring is required to ensure safe anticoagulation and prevent fatal medication errors.

This guideline has been developed to support a safe and clinically effective approach to the management of adult patients in primary care receiving warfarin anticoagulation. The document has been developed in line with national guidelines and alerts.

All staff involved in the prescribing, dispensing, preparing, administration and monitoring of patients on anticoagulant therapy should be fully trained and competent. Further information can be found on the NPSA website – **www.npsa.nhs.uk/health/alerts**.

Information regarding the warfarin care bundle can be found using the following link:

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/SPSPinPC/ES/WarfarinSESP/Pages/WarfarinBundle.aspx

Initiating warfarin therapy

Baseline investigations

Before initiating warfarin anticoagulation request the following baseline investigations
liver function tests
full blood count
clotting screen.

Seek specialist input if any abnormalities.

NB There are no dosing guidelines for patients with an INR ≥ 1.4

Contraindications to warfarin anticoagulation

The following contraindications should be considered before initiating warfarin anticoagulation. The decision to prescribe warfarin should be based on the balance of risk versus benefit for each individual and must be reviewed on a regular basis not less than annually.

Absolute contraindications
(seek specialist advice regarding anticoagulation)
Pregnancy
Allergy to warfarin

Relative contraindications
Haemorrhagic stroke or intracranial haemorrhage*
Acute stroke*
Clinically significant bleeding*
Risk of clinically significant bleeding e.g. recent trauma or surgery, active peptic ulcer*
Uncontrolled hypertension (>180/100mmHg)
Thrombocytopenia (<100)
Significant renal or hepatic impairment
Excess or erratic alcohol intake
Drug abuse
Concurrent medications associated with an increased risk of bleeding
Poor compliance
Dementia
Recurrent falls and seizures

Avoid intramuscular (IM) injections where possible. Intra-articular injections are contraindicated in patients on warfarin.

* These conditions may initially present as an absolute contraindication to any form of anticoagulation but in time the risk-benefit of being on anticoagulation may change. Advice can be sought from haematology or the stroke team if necessary.

Initiating warfarin therapy

Documentation

The following information must be documented in the patient notes and yellow book.

This information should be verbally discussed with the patient at the time of initiation

Indication for treatment
Target INR
Duration of treatment
Name of drug and current dose

Information for patients before starting therapy

Patients and carers should receive both verbal and written information about anticoagulant treatment before initiation of warfarin anticoagulation.

Target INRs and duration of therapy

Note: The following recommendations relate to warfarin anticoagulation in adult males and adult non-pregnant females. For cancer patients refer to separate ECC policies.

Venous Thromboembolism		
Indication	INR Range (Target INR)	Duration
Provoked calf vein thrombosis	2.0-3.0 (target INR: 2.5)	3 months
Provoked proximal DVT/PE	2.0-3.0 (target INR: 2.5)	3 months
Unprovoked proximal DVT/PE	2.0-3.0 (target INR: 2.5)	**Minimum 3 months to indefinite (*seek specialist input*)**
Isolated calf vein DVT, proximal DVT/PE and post-op deep vein thrombosis ***with persistent risk factors***	2.0-3.0 (target INR: 2.5)	***seek specialist input***

Venous Thromboembolism		
Indication	INR Range (Target INR)	Duration
Two or more episodes of unprovoked DVT/PE	2.0-3.0 (target INR: 2.5)	**Indefinite anticoagulation**
Two or more episodes of provoked DVT/PE	2.0-3.0 (target INR: 2.5)	*seek specialist input*
Recurrent DVT/PE on therapeutic anticoagulation at target INR 2.5	3.0 -4.0 (target INR: 3.5)	Indefinite anticoagulation
Recurrence of DVT on therapeutic anticoagulation at INR 3.5	*seek specialist input*	
VTE associated with Antiphospholipid syndrome	2.0-3.0 (target INR: 2.5)	*seek specialist input*

Non-valvular Atrial Fibrillation Paroxysmal or permanent atrial fibrillation		
Indication	INR Range (Target INR)	Duration
All patients with AF who have $CHADS_2$ or CHA_2DS_2-VASc of ≥1	2.0-3.0 (target INR: 2.5)	Long term
AF associated with a) clinical thyrotoxicosis b) non-cerebral thromboembolism	2.0-3.0 (target INR: 2.5)	a) Until controlled b) Long term
Elective cardioversion	2.0-3.0 (target INR: 2.5)	Minimum 3 weeks pre procedure Minimum 4 weeks post procedure; ongoing requirement as directed by cardiologist.

In all patients with AF, risk factors for systemic thromboembolism should be assessed routinely using $CHADS_2$ or CHA_2DS_2-VASc score. Further information can be found in SIGN guideline 129 Antithrombotics: indications and management: **http://www.sign.ac.uk/pdf/SIGN129.pdf**.

*Antiplatelet therapy is sometimes indicated in patients taking warfarin, most commonly in patients with acute coronary syndromes. Options include temporary cessation of warfarin, or co-prescription of an antiplatelet drug. Please seek specialist advice before prescribing antiplatelet therapy for patients on warfarin anticoagulation.

** Patients with evidence of intracardiac thrombus should receive anticoagulation for a minimum of 3 months. Echocardiography is used to guide treatment duration. If patients are considered at ongoing risk, anticoagulation may be continued indefinitely.

Valvular Atrial Fibrillation Heart valve disease		
Indication	INR Range (Target INR)	Duration
Rheumatic mitral valve disease and mitral stenosis	2.0-3.0 (target INR 2.5)	Long term

Valvular Heart disease Mechanical (metallic) heart valve prostheses Target INR depends on site of valve replacement, position and manufacturer. Target INR and range should be stipulated by the cardiologist/cardiac surgery team		
Indication	INR Range	Duration
Mechanical heart valves Aortic valve Mitral valve	Surgeon dependant - As per guidance from cardiac surgery unit 2.5 – 3 2.5 – 3.5 (specific INR target recommended by surgeon)	Lifelong – follow guidance from cardiac unit

Other indications		
Indication	INR range (Target INR)	Duration
Patients requiring anticoagulation and antiplatelet therapy *	2.0-3.0 (target INR 2.5)	As prescribed by consultant cardiologist/stroke physician/haematologist
Intracardiac thrombus**	2.0-3.0 (target INR 2.5)	At least 3 months as prescribed by cardiology

Dosage adjustments
Computer dosing decision software is recommended for dosing:
http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/SPSPinPC/SESP1617/Pages/WarfarinResources.aspx
If decision software not available refer to Appendix 3

Drug Interactions

Many drugs have the potential to interact with warfarin. Drugs known to increase the anticoagulant effect include amiodarone, simvastatin, omeprazole and most broad spectrum antibiotics (especially ciprofloxacin, co-trimoxazole, clarithromycin and metronidazole). Drugs known to reduce the anticoagulant effect include phenytoin, phenobarbitone, carbamazepine and rifampicin. A full and comprehensive list of interactions can be found in the British National Formulary available online at **www.bnf.org** or from the Summary of Product Characteristics available via **www.medicines.org.uk**.

Alternative therapies also have the potential to interact with warfarin and increase the bleeding risk with no effect on INR. Assume an interaction unless proven otherwise.

Diet and warfarin
Foods rich in vitamin K may interfere with warfarin metabolism e.g. leafy vegetables, liver, broccoli, brussel sprouts; patients should be advised to have consistent intakes of these foods.
Grapefruit and cranberry juice may affect warfarin metabolism
All patients should be advised to moderate their alcohol intake while on warfarin and avoid binge drinking
Acute excess intake of alcohol may result in an increase in the effect of warfarin

Additional Information:

Antiplatelet therapy and concurrent warfarin anticoagulation There is an increased risk of haemorrhage with aspirin or clopidogrel in combination with warfarin. Antiplatelet therapy is sometimes indicated in patients taking warfarin, most commonly in patients with acute coronary syndromes. Options include temporary cessation of warfarin, or co-prescription of an antiplatelet drug. Please seek specialist advice before prescribing antiplatelet therapy for patients on warfarin anticoagulation.

Subtherapeutic INRs

The need for LMWH bridging needs to be reviewed on a case by case basis.

Bridging anticoagulation is recommended in the following situations:

(i) if the INR becomes significantly sub-therapeutic (i.e.<1.7) within the first month following an episode of venous thromboembolism;
(ii) in patients with non-valvular atrial fibrillation, where the stroke risk is deemed very high, e.g. CHA_2DS_2-VAS_C score >4 (when consideration should be given to conversion to apixaban)
(iii) in patients with a mechanical mitral heart valve.

Please seek specialist advice as required.

Specialist Advice
Specialist advice may be sought in the following circumstances:

Unprovoked venous thromboembolism
Recurrent DVT/PE if target INR > 3.5.
Screening and management of patients with hereditary thrombophilia.
Management of chronic venous insufficiency/post-phlebitic syndrome.
Patient on another vitamin K antagonist – e.g. phenindione, acenocoumarol (nicoumalone).
Peri operative bridging anticoagulation
Pregnancy (See RefHelp for further advice)

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/GP%20Referral%20Guidelines/Documents/Advice%20for%20women%20on%20warfarin%20or%20DOACs.doc

Poor INR control (not due to poor compliance)
Patients with evidence of warfarin resistance.
Patients requiring antiplatelet therapy
Venous thrombosis at atypical sites
Evidence of skin necrosis or purple toe syndrome

Management of Primary Care Dental Patients on Warfarin

Refer to Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs. Dental Clinical Guidance.

http://www.sdcep.org.uk/wp-content/uploads/2015/09/SDCEP-Anticoagulants-Guidance.pdf

Pregnancy

Women of childbearing age receiving warfarin should be warned about the teratogenic and harmful effects of warfarin, especially in early pregnancy. They should be advised to use secure methods of contraception while on warfarin. If they suspect they are pregnant, they should be offered an early pregnancy test. Conversion to low molecular weight heparin prior to conception is possible. Specialist advice should be sought if a woman becomes pregnant unexpectedly or requires conversion to low molecular weight heparin; women on long-term anticoagulation should be referred to pre-pregnancy counselling.

Appendix 1: Rapid anticoagulation (Fennerty Regimen)

Note: This is unlikely to be required in primary care but can be used in patients where rapid anticoagulation is required. This protocol should be bridged with low molecular weight heparin until the INR is therapeutic on two separate occasions. Caution should be taken in the elderly to avoid high loading doses.

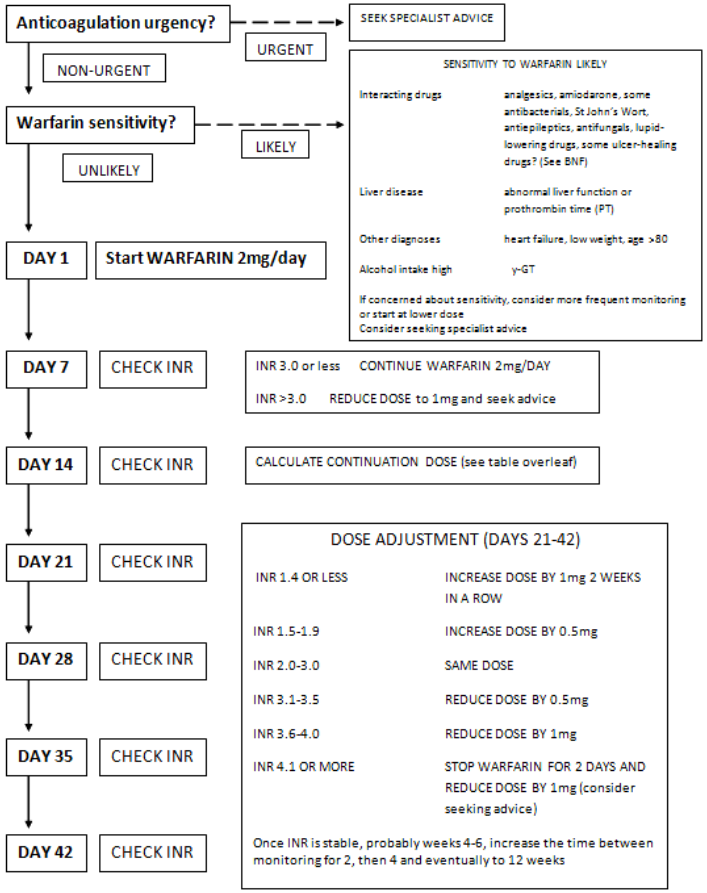
Day	INR – checked am	Warfarin dose (mg) administered pm
1	<1.4	10
2	<1.8	10
	1.8	1
	>1.8	0.5
3	<2.0	10
	2.0-2.1	5
	2.2-2.3	4.5
	2.4-2.5	4
	2.6-2.7	3.5
	2.8-2.9	3
	3.0-3.1	2.5
	3.2-3.3	2
	3.4	1.5
	3.5	1
	4.6-4.0	0.5
	>4.0	OMIT
4	<1.4	>8
	1.4	8
	1.5	7.5
	1.6-1.7	7
	1.8	6.5
	1.9	6
	2.0-2.1	5.5
	2.2-2.3	5
	2.4-2.6	4.5
	2.7-3.0	4
	3.1-3.5	3.5
	3.6-4.0	3
	4.1-4.5	Miss out next day's dose, then give 2mg
	>4.5	Miss out 2 day doses, then give 1mg

Appendix 2: Slow loading regimen

Warfarin may be initiated in the community, usually in older patients with atrial fibrillation, when urgent anticoagulation is not required. This guideline is only intended for initiating warfarin over several weeks in non-acute situations.

Appendix 2: Slow loading regimen
Guidance for Initiating Warfarin in Primary Care

Warfarin may be initiated in the community, usually in older patients with atrial fibrillation, when urgent anticoagulation is not required. This guideline is only intended for initiating warfarin over several weeks **in non-acute situations**.



TABLES FOR PREDICTING MAINTENANCE DOSE AT DAY 14

MALES	
INR at Day 14	Predicated Maintenance Dose
1.0	6mg
1.1-1.2	5mg
1.3-1.5	4mg
1.6-2.1	3mg
2.2-3.0	2mg
>3.0	1mg

FEMALES	
INR at Day 14	Predicated Maintenance Dose
1.0-1.1	5mg
1.2-1.3	4mg
1.4-1.9	3mg
2.0-3.0	2mg
>3.0	1mg

IMPORTANT NOTES ABOUT THE GUIDELINE

- It is only intended for initiating warfarin over several weeks in non-acute situations
- It is based on a validated protocol for similar patients being warfarinised in a hospital outpatient clinic (Oates *et al*. A new regimen for starting warfarin therapy in outpatients. *Br J Clin Pharm* 1998;*46*:157-161).
- It is intended to give an INR of 2.0-3.0 at 6 weeks. Patients with an INR target outside this range may still begin anticoagulation in this way with further adjustments made after 6 weeks.
- INRs are only required at weekly intervals
- The dose of warfarin only changes if the INR is >3.0 or persistently <2.0
- The INR at day 14 predicts the maintenance dose – any subsequent changes are based on routine INR checks at days 21, 28, 35 and 42.
- Once the INR is stable, the time between monitoring can be increased to 2, then 4, and eventually 12 weeks as recommended by the *British National Formulary*.
- Patients should have their liver function tests [including prothrombin time], urea and electrolytes, creatinine and full blood count measured prior to treatment.
- Patients should always be provided with a treatment booklet containing appropriate information about safe use of warfarin.

Further information about oral anticoagulation can be obtained from:

- British Society of Haematology Guidelines (www.b-s-h.org.uk/guidelines/)
- SIGN 129 Antithrombotics: Indications and Management (www.sign.ac.uk/guidelines/fulltext/129/)

Appendix 3: Dose adjustments and Management of Overanticoagulation, Reversal of warfarin

Information on reversing warfarin can be found using the following link:

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Warfarin%20Reversal.pdf

Dose Adjustments, Maintenance Therapy

- Dose adjustments should not be made in isolation – the patient's dosing history needs to be considered at all times.
- Dose adjustment is not required for minor fluctuations of INR as long as the results remain within the patient's target ±0.5.
- Fluctuations of INR outwith the patient's target ±0.5 should always be investigated and corrected where possible. Consider causes such as change in dosage of warfarin, patient compliance, medication profile, change in diet or alcohol intake, initiation of an interacting drug and intercurrent illness.

Practice Point

Changes in warfarin dosage may take several days to affect INR. Frequent dose adjustment is not recommended.

Dose Adjustments, Maintenance Therapy (continued)
Target INR 2.5 ± 0.5

- Relevant patient information (e.g. concurrent treatment, intercurrent illness, compliance) needs to be considered in conjunction with dosing tables.
- 'Dose' refers to daily dose, unless otherwise stated.

INR	Dose adjustment	Next Appointment
1.1 – 1.4	One time dose of additional amount equal to 20% of weekly dose plus usual maintenance dose. Then increase weekly total dose by 20%, and divide this by 7, to get new maintenance dose. Note: this may involve different doses Mon- Fri (eg 5mg) vs Sat-Sun (4mg), or different doses on alternate days (i.e. 3mg/4mg/3mg) e.g. patient on maintenance dose of 5mg – weekly dose = 35mg 20% = 7mg + previous daily dose 5mg Therefore, one time top-up dose = 12mg New daily dose = 35mg +7mg = 42mg ÷ 7 Maintenance dose now 6mg	1 week
1.5 – 1.9	Increase weekly dose by 10% then divide by 7 for new daily dose	1 week
2.0 – 3.0	No change	Refer to Maximum Recall Periods , Maintenance Therapy page 14
3.1 – 3.9	Decrease weekly dose by 10% then divide by 7 for new daily dose	1 week
4.0-5.0	Omit 1 dose. Decrease weekly dose by 10% -20% then divide by 7 for new daily dose	4-5 days
> 5.0	See Management of Overanticoagulation and Bleeding, pages 15-17	

Dose Adjustments, Maintenance Therapy (continued)
Target INR 3.5 ± 0.5

INR	Dose adjustment	Next Appointment
1.1 – 1.4	One time dose of additional amount equal to 20% of weekly dose plus usual maintenance dose. Then increase weekly total dose by 20%, and divide this by 7, to get new maintenance dose. Note: this may involve different doses Mon- Fri (eg 5mg) vs Sat-Sun (4mg), or different doses on alternate days (ie 3mg/4mg/3mg) e.g. Patient on maintenance dose of 5mg – weekly dose = 35mg 20% = 7mg + previous daily dose 5mg Therefore, one time top-up dose = 12mg New daily dose = 35mg +7mg = 42mg ÷ 7 Maintenance dose now 6mg	1 week
1.5 – 1.9	Increase weekly dose by 20% then divide by 7 for new daily dose	1 week
2.0 – 2.9	Increase weekly dose by 10% then divide by 7 for new daily dose	1 week
3.0 – 4.0	No change	Refer to Maximum Recall Periods, Maintenance Therapy page 14
4.1 – 4.9	Decrease weekly dose by 10% then divide by 7 for new daily dose	1 week
5.0-6.0	Omit 1 dose. Decrease weekly dose by 10% -20% then divide by 7 for new daily dose **	4-5 days
>6.0	See Management of Overanticoagulation and Bleeding, pages 15-17	

** Standard risk patients do not require INR reversal at INR 5.0-7.9, but correction should be considered in “high risk” patients by giving Konakion®MM Paediatric phytomenadione 1mg orally

Maximum Recall Periods during Maintenance Therapy

This guidance does not apply to patients with prosthetic heart valves where the maximum recall is 6 weeks. This patient group may need more frequent INRs in the first few weeks following discharge from hospital.

Relevant patient information and dosing/INR history must also be considered when determining timing of next appointment, for example difficulty in achieving initial therapeutic INR should prompt a repeat INR earlier than the 2 weeks recommended period.

Current INR	Next INR check
One INR therapeutic (about 6 weeks after elective induction or at discharge from hospital)	2 weeks
Two INRs therapeutic at two weekly monitoring intervals	4 weeks
Two INRs therapeutic at four weekly monitoring intervals	8 weeks
Two INRs therapeutic at eight weekly monitoring intervals	12 weeks

Management of Overanticoagulation and Bleeding

- Patients must be assessed for signs/symptoms of bleeding.
- Risk factors for bleeding include: history of past bleeding, recent surgery, hypertension, cerebrovascular disease or stroke, serious heart disease or recent myocardial infarction (MI), renal insufficiency, liver disease, other pre-existing bleeding disorder e.g. thrombocytopenia, age > 65 years and frailty, severe anaemia (Hb <10g/L), diabetes, concomitant medications that potentiate bleeding.
- Bleeding that occurs whilst the INR is within the therapeutic range should be investigated for other underlying causes.
- Minor bleeding includes haemoptysis, purpura, unexplained or excessive haematomas, epistaxis and haematuria.
- Major bleeding includes gastrointestinal, intracranial, intra- articular, intraspinal, intraocular or retroperintoneal.
- Dose reduction is not always necessary if a reason for the high INR can be identified e.g. binge drinking.
- The absorption of intravenous (IV) vitamin K_1 preparation given orally is as complete and as rapid as the IV preparation given IV. Therefore IV access may not be required when reversing excess anticoagulation.
- Oral Vitamin K – preparation used is Konakion® MM Paediatric, which comes in a concentration of 2mg/0.2mL. The oral syringes provided with each pack should be used to measure the required volume to be given orally. These syringes explicitly state 1mg and 2mg markings.
- Re-education of patients who are overanticoagulated is crucial. This should include medicines to avoid, what to look out for that suggests overanticoagulation, what to do if this occurs, where to get their INR tested in an emergency.
- Poorly compliant elderly patients may require more frequent monitoring.

Management of Overanticoagulation and Bleeding (continued)
Target INR 2.5± 0.5

- INR 3.1-4.9: refer to maintenance dosage adjustment on page 12
- Patient must be assessed for signs/symptoms of bleeding if overanticoagulated (i.e. INR > 5).
- Reason for anticoagulation and patient risk factors must be considered when deciding on next appointment

INR	Dose adjustment	Next Appointment
5.0 – 6.0	- Omit warfarin for 2 days - Restart warfarin. Reduce weekly dose by 20%, then divide by 7 for a new daily dose **	5 days after restarting warfarin
6.1-8.0	-Stop warfarin -Restart warfarin when INR < 5 -Reduce weekly dose of warfarin by 20% then divide by 7 to get new maintenance dose**	Daily appointmentuntil INR < 5 3-5 days after warfarin restarted
> 8.0 and no bleeding or minor bleeding	- Stop warfarin - Assess patient for risk factors associated with increased risk of bleeding - Consider administering Vitamin K_1 Konakion®MM Paediatric injection 2mg (0.2ml) **by mouth** or **by slow iv injection**. If ≥1 risk factor, consider hospitalisation for overnight observation. Discuss with secondary care. - If INR unchanged or higher the next day, the dose of Vitamin K_1 may be repeated. - Repeat INR can be checked 6 hours or more after the vitamin K_1 has been given. - Restart warfarin when INR < 5 - Reduce weekly dose of warfarin by 20% then divide by 7 to get new maintenance dose	Daily appointment until INR < 5 3-5 days after warfarin restarted
Major bleeding	- Stop warfarin - Resuscitate and transfer to hospital immediately, where specialists will initiate immediate, urgent, warfarin reversal	As directed by specialist care

** Standard risk patients do not require INR reversal at INR 5.0-7.9, but correction should be considered in "high risk" patients by giving Konakion®MM Paediatric phytomenadione 1mg orally

Management of Overanticoagulation and Bleeding (continued)
Target INR 3.5± 0.5

- INR 4.1-5.9: refer to maintenance dosage adjustment on page 13
- Patient must be assessed for signs/symptoms of bleeding if overanticoagulated (i.e. INR > 6).
- Reason for anticoagulation and patient risk factors must be considered when deciding on next appointment

INR	Dose adjustment	Next Appointment
6.1 – 8.0	- Stop warfarin - Restart warfarin when INR<6 - Reduce weekly dose by 20%, then divide by 7 to get new maintenance dose **	Daily appointment until INR <6 3-5 days after warfarin restarted
> 8.0 and no bleeding or minor bleeding	-Stop warfarin - Assess patient for risk factors associated with increased risk of bleeding - Consider administering Vitamin K_1 Konakion®MM Paediatric injection 2mg (0.2ml) **by mouth** or **by slow iv injection**. If ≥1 risk factor, consider hospitalisation for overnight observation. Discuss with secondary care. - If INR unchanged or higher the next day, the dose of Vitamin K_1 may be repeated. - Repeat INR can be checked 6 hours or more after the vitamin K_1 has been given. - Restart warfarin when INR < 6 - Reduce weekly dose of warfarin by 20% then divide by 7 to get new maintenance dose	Daily appointment until INR < 6 3-5 days after warfarin restarted
Major bleeding	- Stop warfarin - Resuscitate and transfer to hospital immediately, where specialists will initiate immediate, urgent, warfarin reversal	As directed by specialist care

** Standard risk patients do not require INR reversal at INR 5.0-7.9, but correction should be considered in "high risk" patients by giving Konakion®MM Paediatric phytomenadione 1mg orally

Contacts and Further Information

Pharmacy Medicines Information
Contact should be with your local pharmacist directly first.

Lothian Medicines Information can be contacted at:
0131 242 2920

Anticoagulant therapy record booklets may be obtained from:
Stockorders.dppaf@apsgroup.com
0131 629 9938

Further information may be obtained from:
British Society of Haematology Guidelines, 4th edition, 2011. http://www.b-s-h.org.uk/guidelines/guidelines/oral-anticoagulation-with-warfarin-4th-edition/

Scottish Intercollegiate Guidelines Network, SIGN 129 "Antithrombotics : indications and management"
www.sign.ac.uk/guidelines/fulltext/129/