Version 4 – January 2016

NHS DORSET CLINICAL COMMISSIONING GROUP POSITION STATEMENT ON ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION

Dorset CCG commissions the use of newer oral anti-coagulants (NOAC / DOAC) in accordance with NICE Technology Appraisals 249, 256, 275 and 355. The drugs hold a green status on the pan-Dorset formulary when used in atrial fibrillation.

1. NICE Technology Appraisals 249, 256, 275 and 355 recommend dabigatran, rivaroxaban, apixaban and edoxaban as options for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (AF). The position of these oral anticoagulant agents and warfarin has been considered by both the cardiology and anti-coagulant sub-groups of the Dorset Medicines Advisory Group and the follow local guidance agreed for the Dorset area.

   Please note:

   - the use of any of the new oral anticoagulants (NOACs) for the prevention of Venous Thromboembolism (VTE) after hip and knee replacement surgery in adults (as covered by NICE Technology Appraisals 157, 170 and 245 respectively) where the full treatment course must be supplied by the specialist service **and**
   - the use of any of the new oral anti-coagulants in the treatment and secondary prevention of pulmonary embolism and deep vein thrombosis (NICE Technology Appraisals 261, 341, 327 and 354)

   is outside the scope of this guidance.

2. Where a diagnosis of atrial fibrillation has been confirmed and oral anticoagulation is appropriate, the advantages and disadvantages of each available option should be discussed with the patient, before a consensus selection is made. Prescribers may find it beneficial to refer to the patient decision aids produced by NICE as part of Clinical Guideline 180 (link) when discussing treatment options with patients.

3. Dabigatran, rivaroxaban, apixaban and edoxaban are locally categorised as GREEN*on the pan-Dorset formulary traffic light list when used for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (AF) in accordance with respective NICE Technology Appraisals.

4. Where a patient with non-valvular AF does not meet the requirements of the respective NICE Technology Appraisals, Dorset CCG would not expect to routinely commission treatment with a NOAC. Warfarin would be the treatment of choice in this circumstance. Where warfarin is not suitable as defined by the criteria in paragraph 11 a newer oral anti-coagulant could be considered. Please note this is likely to mean prescription outside of the product license and has medico-legal implications.

5. It is recognised that an informed discussion between patient and clinician should, where possible, provide the basis upon which an oral anti-coagulant is selected.

6. Clinicians are referred to the decision support tool created by Greater Manchester Clinical Commissioning Group located within appendix 1 to this document for comparative information on the features of rivaroxaban, dabigatran and apixaban.

7. Discussion with a relevant secondary care specialist is recommended prior to initiating therapy in primary care, this may be by telephone or email. They do not need to be referred to secondary care unless that is applicable to the individual patient.

8. Anticoagulation should be offered to patients with a CHA_2DS_2VASc score of 2 or more and considered for men with a CHA_2DS_2VASc score of 1 taking bleeding risks into account. The CHA_2DS_2-VASc risk assessment tool is available as an appendix to this document.

9. Aspirin should not standardly be offered as monotherapy for stroke prevention.

10. This document is for guidance only - all doctors have responsibility for their own prescriptions and have to bear in mind licensing issues as well as evidence base.

11. Patient groups for whom the new oral anti-coagulants are particularly suited:
    - Those with significant, recognised, unwanted side effect(s) of warfarin
    - True allergy/hypersensitivity to warfarin
    - Poor venous access (if finger prick INR testing is unavailable) making INR monitoring problematic
    - Poor INR control with warfarin (INR within treatment therapeutic range (TTR) is <65% (NICE quality Guideline) over the last six months excluding the 3 month initiating period). This information will be available from the service/software in anticoagulation clinics.

    OR in the absence of a known TTR if in the last 6 months of treatment with warfarin (excluding the 3 month initiating period):

    - INR results have been greater than 5 on more than two occasions or an INR result >8
    - INR has been <1.5 on more than two occasions.
    - The INR is unstable, and still requires monitoring every two weeks or less.

12. Non-concordance with warfarin treatment should be excluded as a possible cause for results outside of the target treatment range.

LOCAL GUIDELINES FOR IMPLEMENTATION OF NICE, FOR INITIATION IN SECONDARY CARE

13. If a TIA or stroke occurs on warfarin, with appropriate INR control, and the clinician considers that AF is the cause of the new stroke, a switch to a suitable new oral anticoagulant is recommended. Clinicians are directed to the prescriber support tool developed by Greater Manchester Commissioning Support Unit (GMCSU) which is included as an appendix to this document, or can be accessed here:

    http://gmmmg.nhs.uk/docs/guidance/GMMMG%20NOAC%20prescriber%20decision%20support%20Dec%202013.pdf

14. Patients presenting with AF and very recent acute TIA, where rapid anticoagulation is appropriate, are recommended to initiate a LMWH plus warfarin or a NOAC / DOAC. After 2 months patients could be reassessed and in discussion with a practitioner consider a change to warfarin or whether continuing with the NOAC is the better alternative.

15. For patients who may be considered for cardioversion, an appropriate protocol such as the pan-Dorset guideline for anticoagulation should be followed, including a patient disclaimer regarding personal responsibility for compliance.

16. Patients taking oral anticoagulation should be counselled to always carry a yellow anticoagulant warning card.

17. Patients initiated on warfarin should be supplied with a yellow anticoagulant pack.

SUMMARY OF NICE TECHNOLOGY APPRAISALS

18. NICE TA 355 recommends edoxaban as an option for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation who have one or more risk factors, including:
    - congestive heart failure
    - hypertension
    - diabetes
    - prior stroke or transient ischaemic attack
    - age 75 years or older

19. NICE TA 249 recommends dabigatran as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more of the following risk factors.
    - Previous stroke, transient ischaemic attack (TIA) or systemic embolism
    - Left ventricular ejection fraction below 40%
    - Symptomatic heart failure of NYHA class 2 or above
    - Age 75 years or older
    - Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

20. NICE TA 256 recommends rivaroxaban as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:
    - congestive heart failure
    - hypertension
    - age 75 years or older
    - diabetes mellitus
    - prior stroke or transient ischaemic attack

21. NICE TA275 recommends apixaban as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:
    - Prior stroke or transient ischaemic attack
    - Age 75 or older
    - Hypertension
    - Diabetes mellitus
    - Symptomatic heart failure

22. For people who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in the light of their level of International Normalisation Ratio (INR) control.

23. The decision to start treatment with NOAC should be made after an informed discussion between the clinician and patient about the risks and benefits compared with warfarin.

RATIONALE FOR RECOMMENDATIONS

24. The opinion of the pan-Dorset anticoagulation working group and that of the cardiovascular working group is that where a patient is identified as requiring an oral anticoagulant the clinician should be encouraged to support the patient in selecting the agent which best meets their requirements. The following points should be considered:

    - Warfarin has a longer track record with established risks and benefits
    - The newer agents should not generally be considered to be safer for patients who are felt to be unsuitable for warfarin due to higher risk of haemorrhage e.g. those at high risk of falls. Overdosing with warfarin can be reversed with parenteral vitamin K. Treatments to significantly reverse the clinical effects of dabigatran, rivaroxaban, apixaban and edoxaban should become available during 2016. It is worth noting that the rate of life threatening or fatal bleeding was lower with all four NOACs/DOACs than it was with warfarin even allowing for the lack of a currently available reversal agent for the NOACS. Patients taking warfarin receive regular INR test whereas those taking the new anticoagulant agents do not. Changes in patient condition and poor concordance are therefore likely to be noticed more quickly in warfarin patients. If patient concordance with their medication is likely to be an issue prescribers should take this into consideration.
    - Any drugs with a black triangle drug should be subject to greater vigilance and clinical monitoring. Adverse effects need to be recorded via the yellow card system which is available at www.yellowcard.mhra.gov.uk/

25. CHA_2DS_2VASc is the recommended stroke risk stratification scoring tool, with 'HAS-BLED' being the recommended bleeding risk calculator for anti-coagulated patients with AF. Both risk scoring tools are located in Appendix 2 to this document. The Dorset Clinical Commissioning Group supports the current European Society of cardiology guideline to strongly consider oral anticoagulation in all persons with AF who have a CHA_2DS_2VASc Score >1 (exception female sex alone) where there are no contraindications (or a CHADS2 score >1).

OTHER POINTS FOR CONSIDERATION

26. The trials of dabigatran, rivaroxaban and apixaban were non-inferiority studies. On intention to treat analysis both dabigatran at 150mg bid and apixaban at 5mg bid were superior to warfarin for the prevention of stroke and systemic embolism. There is uncertainty over the superiority of dabigatran in well controlled warfarin patients. NICE however concluded that apixaban was more clinically effective than warfarin for the primary efficacy outcome of reducing stroke and embolism. NICE also commented that edoxaban was as clinically effective as warfarin for the primary efficacy outcome of reducing stroke (ischaemic and haemorrhagic) and systemic embolism, and had nearly half the rate of haemorrhagic stroke events compared to warfarin. Reduced haemorrhagic stroke rates compared to warfarin are seen with all the newer agents.

27. The submission on dabigatran to the FDA showed a greater benefit in people with poor INR control than in those with well controlled INR, greatest benefit being in those in the lowest quartile of INR control. The NICE evidence review group (ERG) highlighted that in people with good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran. The ERG carried out an exploratory cost effectiveness analyses by subgroups, for people with INR range 100% in target range, the ICER was £60,895/QALY gained for dabigatran 150mg bd, the 110mg dose was dominated by warfarin (dabigatran had greater costs but lower health benefits). Both dabigatran and rivaroxaban dominated warfarin in analyses of individuals with poorly controlled INR.

28. In the RE-LY trial at a dose of 150mg of dabigatran there was a statistically significant difference in the number of strokes, absolute risk reduction of 1.2% (NNT 83), equating to a cost of £116,166 to prevent one additional stroke.

29. Dabigatran is sensitive to moisture and should not be stored in compliance aids such as dosette boxes. Prescribers are reminded that the use of compliance aids is not encouraged unless a suitable assessment tool has been completed, preferably by a pharmacist.

PATIENT SAFETY

30. Patients should be advised to carry an appropriate anticoagulant alert card. The recommendation is to use a yellow novel anticoagulation alert card as located in appendix 3.

31. Patients should be advised that in the event of significant acute illness or signs of bleeding to stop their anticoagulant medication and seek urgent medical advice.

32. Patients and carers must have a copy of the patient information leaflet for the drug prescribed. Community pharmacies or dispensing doctors who supply the drug should ensure that the patient is supplied with a copy of the leaflet.

33. Patients need to understand the benefits and risks of the new anticoagulants and warfarin through fully informed decision making – a copy of this guidance may be appropriate for some patients.

34. For all NOACs/DOACs baseline renal and liver function must be undertaken prior to use as a minimum standard and preferably annually thereafter. Patient 75 years or over and those with

a suspected decline in renal function should have their renal function checked at least once a year during continued treatment. Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications) and when other drugs with renal effects are introduced or prescribing altered.

CONSIDERATIONS FOR SPECIFIC INDICATIONS

35. Prescribers are directed to the Prescribing Support Tool produced by the Greater Manchester Clinical Support Unit as referenced in Appendix 1, which compares individual drugs and relevant factors to consider when initiating treatment with a NOAC/DOAC.

36. When considering which of the new oral agents to prescribe with a patient the decision should be based on selecting the most cost effective and evidence based product and be in accordance with the license and appropriate NICE technology appraisals.

37. As the new agents are not subject to INR monitoring, there is no ready means to determine if a patient is concordant with their medication, prescribers should therefore also take into consideration whether the patient is likely/able to comply with their medication, prior to prescribing, this may require secondary care clinicians contacting their GP colleagues for advice on the patient's home situation. This should be a two way discussion.

38. NOACs/DOACs should be initiated by competent prescribers, which includes but is not limited to doctors, other than training grades, in both primary and secondary care and non-medical prescribers when prescribing in conjunction with a suitable clinical management plan under direction from an identified doctor.

REFERENCES

1. NICE TA 249 Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

http://publications.nice.org.uk/dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-ta249

2. NICE TA 256 Atrial fibrillation (stroke prevention) – rivaroxaban

http://publications.nice.org.uk/rivaroxaban-for-the-prevention-of-stroke-and-systemic-embolism-in-people-with-atrial-fibrillation-ta256

3. NICE TA275 Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

http://publications.nice.org.uk/apixaban-for-preventing-stroke-and-systemic-embolism-in-people-with-nonvalvular-atrial-fibrillation-ta275

4. Peninsula Heart & Stroke Network Guidance- New oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation
www.plymouthformulary.nhs.uk/includes/documents/10-Peninsula-Network-Guidance-on-New-Anticoagulants-May2012-final.pdf

5. Summary of product characteristics for Dabigatran (Pradaxa ®) 23/07/2014

www.medicines.org.uk/EMC/searchresults.aspx?term=dabigatran+etexilate+mesilate&searchtype=QuickSearch

6. Summary of product characteristics for rivaroxaban (Xarelto ®) 18/08/2014

www.medicines.org.uk/EMC/searchresults.aspx?term=Rivaroxaban&searchtype=QuickSearch

7. Summary of product characteristics for apixaban (Eliquis®) 22/07/2014

www.medicines.org.uk/emc/medicine/27220/SPC/Eliquis+5+mg+film-coated+tablets/

8. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. EuropeanHeart RhythmAssociationPractical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation.Europace 2013;15:625-51
http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Documents/EHRA-NOAC-Practical-Full-EPEuropace-2013.pdf

9. NICE Implementation Collaborative. Consensus: Supporting local implementation of NICE guidance on use of the novel (non-Vitamin K antagonist) oral anticoagulants in non-valvular atrial fibrillation; June 2014. Available at http://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-nic-consensus-statement-on-the-use-of-noacs2 Accessed July 2014.

10. Gregory Y. H. Lip, MD; Robby Nieuwlaat, PhD; Ron Pisters, MD; Deirdre A. Lane, PhD; Harry J. G. M. Crijns, MD. Refining Clinical Risk Stratification for Predicting Stroke and

Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: The Euro Heart Survey on Atrial Fibrillation *Chest.* 2010;137(2):263-272.

11. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. CHEST 2010;138:1093-1100.

12. J.Cheung. Prescriber Decision Support of New Oral Anti-Coagulants (NOACs). Medicines Management, Greater Manchester Commissioning Support Unit. December 2013. Available at: http://gmmmg.nhs.uk/docs/guidance/GMMMG%20NOAC%20prescriber%20decision%20support%20Dec%202013.pdf Accessed 20 August 2014

Appendix 1

NOAC Prescribing Decision Support from GMCSU available at:

http://gmmmg.nhs.uk/docs/guidance/GMMMG%20NOAC%20prescriber%20decision%20support%20Dec%202013.pdf

NOACs-Prescribing GMCSU.pdf

Appendix 2

CHA_2DS_2VASc[11] risk assessment tool

Feature	Score
Congestive Heart Failure	1
Hypertension	1
Age >75 years	2
Age between 65 and 74 years	1
Stroke/TIA/TE	2
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	1
Diabetes mellitus	1
Female	1

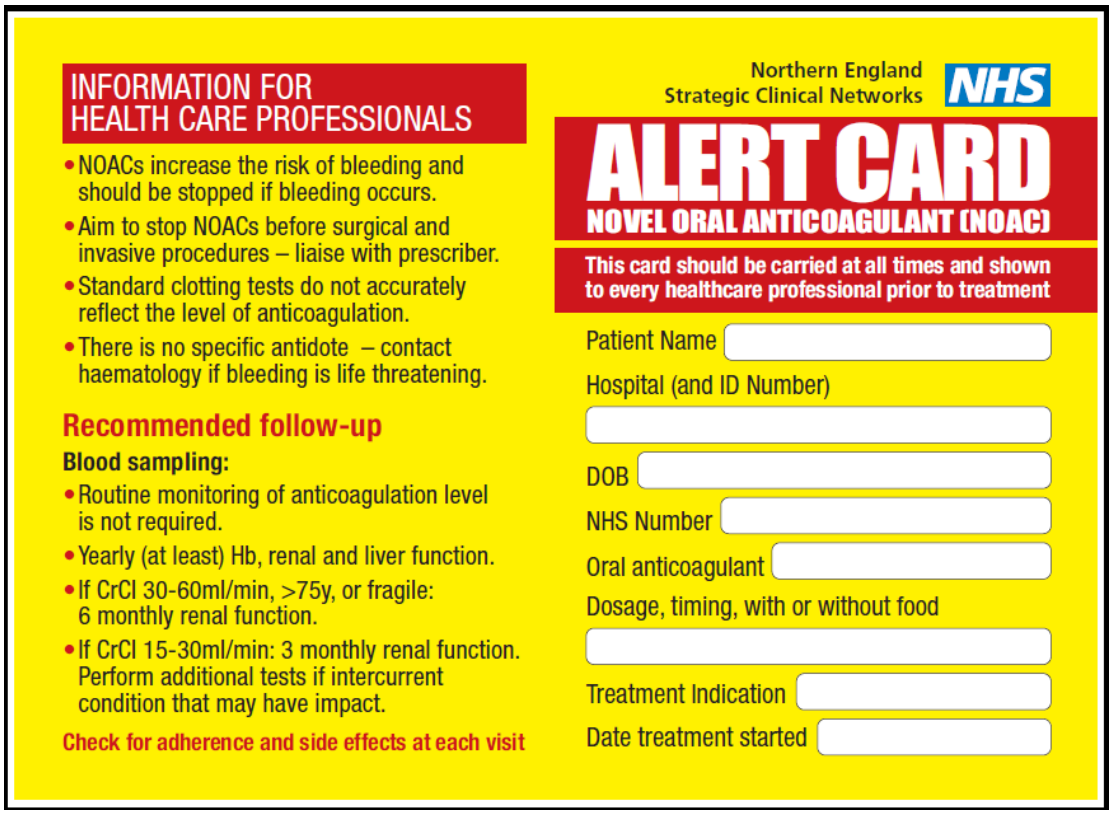
HASBLED[12] bleeding risk assessment tool

Feature	Score
Hypertension (systolic >160mHg)	1
Abnormal liver or renal function	1point for each
Stroke history	1
Bleeding predisposition	1
Labile INR	1
Elderly (>65yo)	1
Illicit drug / alcohol abuse	1 point for each

Score of ≥3 indicates a one year risk of bleeding (intracranial bleed/bleed requiring hospitilisation/Hb drop of 2g/L or needing transfusion) on anticoagulation is sufficient to justify caution or more regular review

Appendix 3

Alert card example for patients taking a NOAC/DOAC



INFORMATION FOR HEALTH CARE PROFESSIONALS

- NOACs increase the risk of bleeding and should be stopped if bleeding occurs.
- Aim to stop NOACs before surgical and invasive procedures – liaise with prescriber.
- Standard clotting tests do not accurately reflect the level of anticoagulation.
- There is no specific antidote – contact haematology if bleeding is life threatening.

Recommended follow-up

Blood sampling:

- Routine monitoring of anticoagulation level is not required.
- Yearly (at least) Hb, renal and liver function.
- If CrCl 30-60ml/min, >75y, or fragile: 6 monthly renal function.
- If CrCl 15-30ml/min: 3 monthly renal function. Perform additional tests if intercurrent condition that may have impact.

Check for adherence and side effects at each visit

Northern England Strategic Clinical Networks

NHS

ALERT CARD

NOVEL ORAL ANTICOAGULANT (NOAC)

This card should be carried at all times and shown to every healthcare professional prior to treatment

Patient Name

Hospital (and ID Number)

DOB

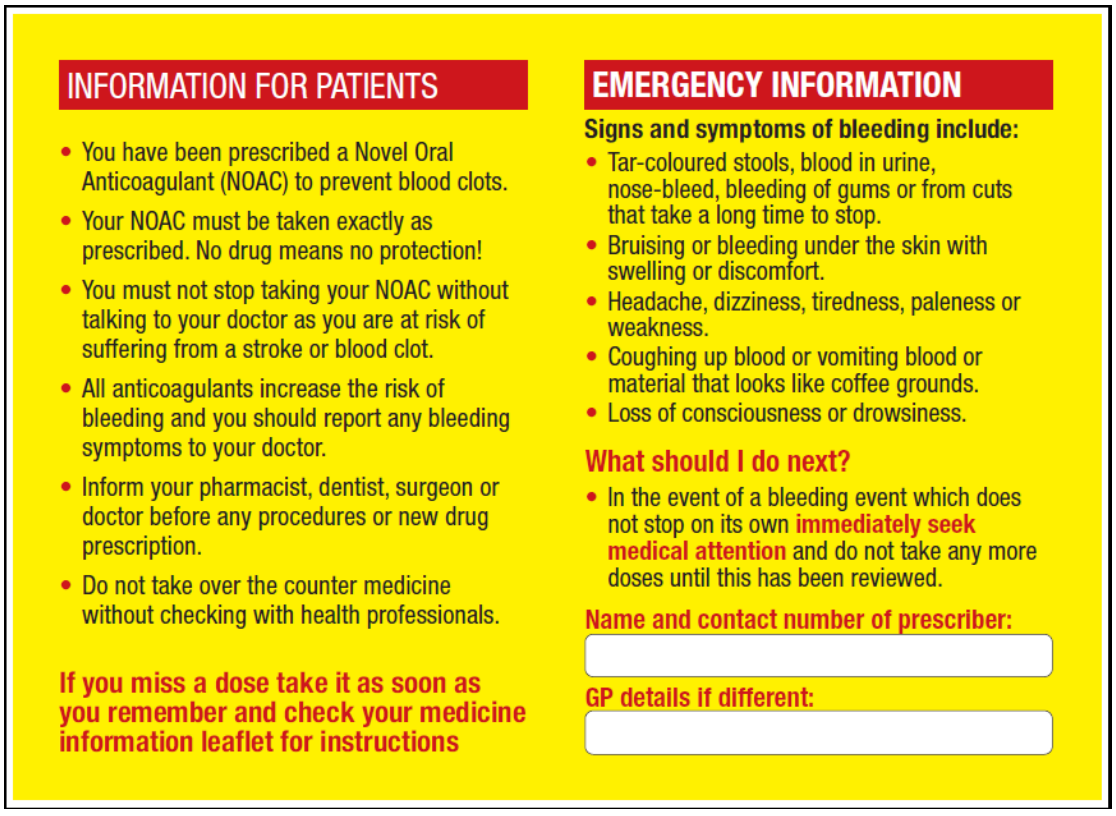
NHS Number

Oral anticoagulant

Dosage, timing, with or without food

Treatment Indication

Date treatment started



INFORMATION FOR PATIENTS

- You have been prescribed a Novel Oral Anticoagulant (NOAC) to prevent blood clots.
- Your NOAC must be taken exactly as prescribed. No drug means no protection!
- You must not stop taking your NOAC without talking to your doctor as you are at risk of suffering from a stroke or blood clot.
- All anticoagulants increase the risk of bleeding and you should report any bleeding symptoms to your doctor.
- Inform your pharmacist, dentist, surgeon or doctor before any procedures or new drug prescription.
- Do not take over the counter medicine without checking with health professionals.

If you miss a dose take it as soon as you remember and check your medicine information leaflet for instructions

EMERGENCY INFORMATION

Signs and symptoms of bleeding include:

- Tar-coloured stools, blood in urine, nose-bleed, bleeding of gums or from cuts that take a long time to stop.
- Bruising or bleeding under the skin with swelling or discomfort.
- Headache, dizziness, tiredness, paleness or weakness.
- Coughing up blood or vomiting blood or material that looks like coffee grounds.
- Loss of consciousness or drowsiness.

What should I do next?

- In the event of a bleeding event which does not stop on its own **immediately seek medical attention** and do not take any more doses until this has been reviewed.

Name and contact number of prescriber:

GP details if different: