APPENDIX G

NHS Surrey

Surrey and Sussex NHS Healthcare NHS Trust

WORKING IN PARTNERSHIP WITH

Information sheet

Rivaroxaban (Xarelto®) 15mg and 20mg Capsules

FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

Surrey Prescribing Clinical Network classification: **Green**

A consensus group met on 9th May 2012 to make recommendations around the use of new oral anticoagulants (dabigatran and rivaroxaban) for stroke prevention in atrial fibrillation. It was agreed that initiation of these drugs would be appropriate in primary care and given a **GREEN** status on the Traffic Light System. It was also felt that an information sheet would be useful in instances where these drugs were not initiated in primary care to ensure that agreed discussions with patients have occurred to ensure a consistent approach across the healthcare economy. This information sheet is available on the internet (http://www.app.surreyhealth.nhs.uk/gpview/default.html) forming part of Surrey PCT's Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter.

RESPONSIBILITIES and ROLES

Surrey Prescribing Clinical Network (PCN) recommendation
• The focus of AF management should be to identify patients with AF and undertake stroke risk assessment using the $CHADS_2$ or CHA_2DS_2–VASc risk assessment tool. Patients with a $CHADS_2$ score ≥ 2 or $CHADS_2$ score 1 and considered high risk should be initiated on warfarin in the first instance, unless contraindicated • Warfarin remains the agent of choice for the prevention of stroke and systemic embolism in AF. Patients currently stable on warfarin therapy should not be considered for a switch to a new oral anticoagulant • Warfarin anticoagulant services should be reviewed to ensure they deliver a high quality standard of care and meet the needs of patients who have difficulty complying with the specific monitoring requirements of warfarin therapy • New oral anticoagulants (NOACs) should be considered as an alternative to warfarin for stroke prevention in AF in patients who: ○ have a warfarin allergy or have an absolute contraindication to warfarin ○ have an ischaemic stroke whilst stable on warfarin and other treatment options including increasing the INR target range or adding in antiplatelets have been considered ○ are intrinsically unstable on warfarin after an adequate trial (usually at least 3 months) despite: - being adherent to warfarin monitoring and lifestyle requirements AND - evidence of compliance with drug therapy AND - attempts have been made to optimise warfarin treatment e.g. patients with co-morbidities requiring frequently co-prescribed medications that interact with warfarin • Aspirin (with or without clopidogrel) is not a suitable alternative to warfarin or NOACs in patients with atrial fibrillation and a CHADS2 score ≥ 2, as it offers significantly less protection against stroke. Aspirin (with or without clopidogrel) should only be considered for such patients where warfarin and NOACs cannot be used due to allergy or contraindications
Responsibilities of initiating clinician
1. Rivaroxaban should only be recommended in line with the PCN recommendation above 2. In making the recommendation the initiating clinician must ensure that an informed discussion with the patient and/or their carer has been conducted covering the risks and benefits of prescribing rivaroxaban compared with warfarin or other anticoagulants for stroke prevention in atrial fibrillation.
Patient's / Carer's roles
1. Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment. 2. Share any concerns in relation to the treatment. 3. Tell the specialist or GP of any other medication being taken, including over-the-counter products. 4. Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP.

Supporting Information - **This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.**

www.medicines.org.uk

Rivaroxaban is a black triangle drug - any adverse effects must be reported to the MHRA

Licensed indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as:

- congestive heart failure
- hypertension
- age ≥ 75 years
- diabetes mellitus
- prior stroke or transient ischaemic attack

Dosage and administration

- ADULT over 18 years - 20 mg once daily
- In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment - 15 mg once daily
- No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min)
- No dose adjustment required in the elderly population

MISSED DOSE

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose

METHOD OF ADMINISTRATION

For oral use. The tablets are to be taken with food

Contraindications and Cautions

Contra-indications	Cautions
• Hypersensitivity to the active substance or to any of the excipients. • Clinically significant active bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C • Patients with creatinine clearance < 15 ml/min • Pregnancy and breast feeding • Patients with prosthetic valves	• Recent surgery • Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs) • Bleeding disorders • Active or recent gastro-intestinal ulceration • Severe hypertension • Vascular retinopathy • Concomitant use of drugs that increase risk of bleeding • Recent intracranial or intracerebral haemorrhage • Intraspinal or intracerebral vascular abnormalities • Bronchiectasis or history of pulmonary bleeding •

Drug Interactions: See overleaf for details of drug interactions including contraindicated drug therapies

Side Effects - See BNF/SPC for full details

The most common adverse effects of rivaroxaban are nausea; haemorrhage; *less commonly* constipation, diarrhoea, dyspepsia, dry mouth, vomiting, hypotension, oedema, tachycardia, thrombocythaemia, syncope, dizziness, headache, renal impairment, pain in extremities, pruritus, and rash; jaundice also reported

Special warnings and precautions for use

a) Haemorrhagic risk

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Management of bleeding

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable

b) Hepatic Effects

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

c) Renal Effects

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min)

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment dose should be reduced to 15 mg once daily.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

Drug Interactions – Please see BNF/SPC for full details

Interacting Drug / Drug Class	Details and Action to be Taken
Ketoconazole Itraconazole Posaconazole Voriconazole Ritonavir	Increase plasma concentration of rivaroxaban. Use contraindicated with rivaroxaban
Rifampicin	Plasma concentration of rivaroxaban reduced by rifampicin
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Saquinavir Tipranavir	Manufacturer of rivaroxaban advises avoid concomitant use with tipranavir
Anticoagulants	Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants
Antiplatelet drugs / NSAIDs / Aspirin	Manufacturer advises care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk.
CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort)	Strong CYP3A4 inducers should be co-administered with caution as they may lead to reduced rivaroxaban plasma concentrations
Dronedarone	Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

References
- BNF, March 2012
- SPC Rivaroxaban (Xarelto®) Bayer plc 2012 Accessed May 23rd 2012 at http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/