NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

COVID-19 - Anticoagulant Update: April 2020

Switching Patients from Warfarin to Rivaroxaban

(within licensed indications)

Background

Due to current unprecedented pressures on the Cambridgeshire and Peterborough healthcare system, our local haematology specialist colleagues in the Cambridge University Hospital Foundation Trust and Royal Papworth Hospital and North West Anglian Foundation Trust have advised to switch all eligible patients from warfarin to rivaroxaban, **who meet an indication within the licensing of rivaroxaban. People who are not included within the license should not be switched without specialist input.**

National guidance has been released which recommends a slightly different approach. This can be utilised if practices prefer, however the following has also been agreed as a suitable approach by local specialists.

National Guidance:
https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627

Exclusions and cautions:

Patients **not suitable** for rivaroxaban - (full details at SPC here):

a. Recorded hypersensitivity to the active substance or to any of the excipients
b. Creatinine clearance < 15 ml/min (contraindicated)
c. For age <18 years (not licensed)
d. Patients who have hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including people who have cirrhosis with Child-Pugh B (moderate impairment) or C (severe impairment).

Special warnings and precautions for use – seek specialist advice to determine best alternative treatment option (if any).

1. **Patients with the following valve problems:**

   Direct oral anticoagulants (*DOACs)* are <u>CONTRA-INDICATED</u> in patients with:

   1. **Moderate to severe mitral stenosis**
   2. **Metallic and prosthetic heart valves**
   3. **Severe mitral regurgitation with a dilated left atrium**

   Rivaroxaban are **<u>CONTRA-INDICATED</u> for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR).**

   Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population.

Patients with a prior history of rheumatic fever but that do not have valvular heart disease as above may have DOAC.

2. **Patients with antiphospholipid syndrome:**
   Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.

3. **Patients with non-valvular atrial fibrillation who undergo PCI with stent placement.**

4. **Interaction with other medicinal products:**
   The use of rivaroxaban is **not recommended** in patients receiving concomitant systemic treatment with **azole-antimycotics** (such as ketoconazole, itraconazole, voriconazole and posaconazole) or **HIV protease inhibitors** (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk.

   Ask the person if they have been taking any other medicines, including any bought over the counter. The SPC for rivaroxaban advises considering if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

5. **Patients with a target INR >2.5 (i.e. high target INR patients)**

6. **Patients with VTE at unusual sites (e.g. cerebral venous sinus thrombosis)**

7. **Pregnancy or breastfeeding**

Recommendation

This aid memoire only refers to switching suitable warfarin patients to rivaroxaban, a Direct Oral Anticoagulant (DOAC) within its licensed indications.

Other DOACs are available and supported by NICE Technology Guidance, and may be considered where the clinician has clinical experience of these, after checking their respective Summaries of Product Characteristics (SPC) available HERE, as licensing and dosing information may vary.

Our system specialist haematology clinician's advice for switching **suitable** patients from warfarin to rivaroxaban is as follows:

Patient should stop taking warfarin for 72 hours before starting rivaroxaban.

Rationale: this 72 hours rationale is based on usual protocol for surgical patients in secondary care where for bridging with Low Molecular Weight Heparin (LMWH), warfarin is stopped at day 5 before surgery and LMWH is started at day 2 i.e. 72 hours (3 days) interval. This in turn causes the INR to be low enough that initiating rivaroxaban should not be an issue.

The rivaroxaban SPC here also advises when converting patients from warfarin therapy to rivaroxaban depending upon the indication for use:-

- Atrial fibrillation patients - discontinue warfarin and start rivaroxaban when INR≤ 3.0.

- DVT, PE and prevention of recurrence - discontinue warfarin and start rivaroxaban when INR is ≤ 2.5.

However, monitoring INR in these unprecedented times might not be a practical option for either primary or secondary care, hence the 72 hours interval.

Initiating treatment

- **Start rivaroxaban at the dose specified in the SPC** here **particularly with reference to the renal function** *(table below).*

  Rationale: NICE CKS here advice is that the **renal and liver function tests, and a full blood count should be performed at the start of rivaroxaban treatment**. *Please note baseline clotting screen is not considered necessary as the patient is already on warfarin.*
  GP should arrange these tests in primary care.

  Patients / carers must be counselled before the switch is undertaken.

Dosing recommendations

	Licensed Indications	Dosage	
Warfarin[1]	Prevention of stroke and systemic embolism	As per INR	
	Prophylaxis and treatment of venous thrombosis and pulmonary embolism		
	Prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation		
	Transient cerebral ischaemic attacks		
Rivaroxaban[2]	**Licensed Indications**	**Dosage**	
		Normal renal function or mild impairment (CrCl 50-80ml/min)	**Moderate renal impairment (CrCl 15-49ml/min)**
	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.	20 mg ONCE daily	15 mg ONCE daily
	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) **– if newly initiated anticoagulation.**	15 mg TWICE daily for 21 days then maintenance dose of 20mg once daily	15 mg TWICE daily for 21 days then maintenance dose of 15mg once daily
	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) **– if switching from warfarin**	20mg once daily	15mg once daily
	Prevention of recurrent DVT and PE in adults	10mg ONCE daily*	10mg ONCE daily*

** In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10mg once daily, a dose of rivaroxaban 20 mg once daily should be considered (dose adjustment needed in renal impairment see SPC).*

Different weight categories: The SPC advises 'body weight, > 120 kg, had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.'

For patients with a low body weight ≤60kg, whilst the SPC advises that no dose adjustment is necessary for rivaroxaban, local specialist opinion is that 30 mg edoxaban once daily for non-valvular

atrial fibrillation and venous thromboembolism could be considered as a suitable alternative. For full details, including other considerations and edoxaban contraindications see SPC here.

Dermatological reactions:
Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (*see section 4.8 of the SPC* here). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions).

Ongoing clinical monitoring to be carried out by the GP:

NICE CKS here advises the following:

- Although there is no need for regular blood tests to monitor the international normalized ratio (INR), people taking rivaroxaban require regular follow up and monitoring.

- **Ideally the person should be assessed every 3 months in order to:**
  - Assess compliance to treatment and to reinforce advice regarding the importance of a regular dosing schedule.
  - Enquire about the presence of any adverse effects such as bleeding and anaemia (as advised by SPC).
  - Assess for the presence of thromboembolic events (e.g. symptoms of stroke, or breathlessness, which may suggest a pulmonary embolism).
    - For more information, see the CKS topics on Stroke and TIA, and Pulmonary embolism.

- **Once treatment has started, repeat the renal and liver function tests and the full blood count at least once a year.**
  - If renal function has declined, review treatment, as rivaroxaban may need to be stopped or a lower dose may be required.
    - For more information, see dose of rivaroxaban.
  - If there is an unexplained fall in haemoglobin and/or haematocrit, occult bleeding may be present. Rivaroxaban can cause bleeding from any site.

- **Repeat renal function tests:**
  - Every six months if the person has a creatinine clearance (CrCl) between 30–60 mL/min.
  - Every three months if the person has a CrCl of 15–30 mL/min.
- **Renal and liver function tests should be performed more often if there is an intercurrent illness that may impact renal or hepatic function.**

According to the rivaroxaban SPC here - INR values will be falsely elevated after the intake of Xarelto and therefore should not be used.

Further information for patients to support counselling can be found via the links below:

Manufacturers PIL: https://www.medicines.org.uk/emc/product/2793/pil
NHS choices link: https://www.nhs.uk/medicines/rivaroxaban/
Cambridgeshire and Peterborough PIL link: here

References:

1. https://www.medicines.org.uk/emc/product/3064/smpc
2. https://www.medicines.org.uk/emc/product/2793/smpc
3. https://cks.nice.org.uk/anticoagulation-oral#!scenarioRecommendation:38