Apixaban, edoxaban or rivaroxaban (Amber TLS)

RUH - Shared Care Guidelines: For the OFF-LABEL treatment of cancer associated thrombosis (see NICE NG158)

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of **apixaban, edoxaban or rivaroxaban for the treatment of cancer associated thrombosis (CAT)** are shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with the condition are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Initiate treatment and provide at least 28 days' supply. The choice of DOAC (apixaban, edoxaban or rivaroxaban) will be made by the specialist on a case by case basis.
2	Discuss the benefits and side effects of treatment with the patient. **NICE NG158 notes that most anticoagulants do not currently have a marketing authorisation for the treatment of thrombosis in people with active cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.**
3	Ask the GP whether he or she is willing to participate in shared care, and agree with the GP as to who will discuss the shared care arrangement with the patient.
4	Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.
5	Provide monitoring details.
6	Review the patient's condition and monitor response to treatment regularly where indicated.
7	Give advice to the GP on when to stop treatment.
8	Report adverse events to the MHRA.
9	Ensure that clear backup arrangements exist for GPs to obtain advice and support.

	General Practitioner responsibilities
1	Reply to the request for shared care as soon as practicable.
2	Prescribe medicine at the dose recommended.
3	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
4	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
5	Stop treatment on the advice of the specialist.
6	Report adverse events to the specialist and MHRA.

	Patient's role
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Share any concerns in relation to treatment with medicine.
3	Report any adverse effects to the specialist or GP whilst taking the medicine in particular signs of bleeding including blood in urine, black tarry stools, coughing up blood, excessive bruising or nose bleeds. Patients should also monitor and report any signs of recurrent or worsening of blood clots including: new/worsening swelling, pain, redness or heat in arm/leg or shortness of breath, chest pain or coughing up blood.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Email address:
Specialist: Nathan Hutchinson-Jones (Lead Pharmacist for Thrombosis and Anticoagulation)	Haematology secretaries	7164	Ruh-tr.AnticoagulationTeam@nhs.net
Hospital Pharmacy Dept. Royal United Hospital, Bath	Meds Information 01225 824633	-	Ruh-tr.medicinesinformation@nhs.net
RUH Anticoagulation team (includes Haematology CAT clinic)	Consultant Connect	-	Ruh-tr.AnticoagulationTeam@nhs.net Preferred contact option
Other: Acute Oncology Team	Consultant Connect	-	-

SUPPORTING INFORMATION

Summary of condition and licensed indications

The medicine is indicated for:

- Treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)
- DOACs (specifically apixaban, edoxaban or rivaroxaban) are an alternative to low molecular weight heparin (LMWH) for the treatment of cancer associated thrombosis (CAT) in specific patients with a low risk of bleeding and where there are no anticipated drug-drug interactions with their anti-cancer therapy or other contraindication.
- DOACs are an option that can be considered for patients with active cancer as per recommendations in NICE NG158 but none of them are currently licensed specifically for this patient group. Phase 3 clinical trials have shown that DOACs are non-inferior to LMWHs but at the cost of increased bleeding risk in certain types of cancer. Apixaban appears to show a more favourable bleeding risk that is comparable with LMWH; however the study was not powered sufficiently to make definite conclusions regarding bleeding risk. Caution should still be used when using DOACs including apixaban in cancer patients with a high risk of bleeding.

Treatment Aims (Therapeutic plan)

DOACs offer a number of benefits *vs*. LMWH:

1. DOACs can be administered orally instead of requiring to be given via subcutaneous injection.
2. DOACs do not routinely require as much monitoring as LMWH.
3. DOACs do not cause heparin induced thrombocytopenia.

Treatment Schedule (including dosage and administration)

Dosing schedule and routine monitoring requirements are the same as for use in non-cancer patients. Some cancer patients may require additional monitoring as a result of their cancer diagnosis or anti-cancer therapy at the request of the specialist. Most patients will require at least 6 months of treatment. In the presence of active malignancy, anticoagulation should be continued beyond 6 months, as advised by the specialist, after discussion with the patient and assessment of the bleeding risk. Reduced intensity anticoagulation may be appropriate beyond 6 months. Apixaban and rivaroxaban are both licenced at a lower dose of 2.5mg TWICE daily and 10mg ONCE daily respectively beyond 6 months for the prevention of recurrent venous thromboembolism (VTE) in non-cancer patients. Edoxaban is also available at a lower dose of 30mg ONCE daily, however it is not licenced specifically for the prevention of recurrent VTE beyond 6 months in non-cancer patients unless a patient's weight is <60kg and/or GFR <50ml/min.

Patients who have had a below knee DVT and/or whose cancer is in remission and is asymptomatic may be able to stop anticoagulation after 3 months, as advised by the specialist.

PICC line associated DVT: If the line remains in situ the patient should be anticoagulated for at least 3 months and/or until line removal. If the line is removed the patient should be anticoagulated for at least a further 6 weeks.

All patients with CAT under the care of the RUH should be referred to the Haematology CAT telephone clinic (see 'Back up advice and support' section above for contact details). Patients should receive a follow up appointment at 1, 3 and 6 months post diagnosis.

The choice of DOAC (apixaban, edoxaban or rivaroxaban) will be determined by the specialist on a case by case basis and provided there are no contra-indications as below. Patients should receive an initial 4 week supply from secondary care/ specialist post diagnosis. Some patients may initially be treated and supplied with LMWH and switched to a DOAC later on the advice of a specialist. LMWH for the treatment for CAT is also part of a shared care agreement with primary care (**See link here**).

Contra-indications and precautions for use

Usual C/I as per SPC/ BNF – refer to specialist if needed.

Cancer patients with a high risk of bleeding and who should be considered for treatment with LMWH rather than a DOAC include patients with:

- GI cancers (particularly upper GI) e.g. oesophageal or gastric cancer
- Urothelial cancers

Other reasons for using a LMWH rather than a DOAC may include:

- History of GI bleeding
- Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake
- Concerns for GI absorption (feeding tubes, gastric or bowel resections)
- Likely thrombocytopenia expected secondary to cancer/ anti-cancer treatment
- Pancreatic cancer
- Previous recurrent VTE on a DOAC or LMWH
- Patients with a primary brain tumour or brain metastases
- Anticipated interaction with anti-cancer therapy (see list of possible interacting agents below).

Side-effects

Side-effects of DOACs are as per BNF/ SPC. Contact the relevant specialist if the patient develops any side-effects and advice is needed on a suitable alternative for anticoagulation. Edoxaban and rivaroxaban have black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Monitoring

Monitoring requirements are as per current use in non-cancer patients. Additional monitoring requirements (e.g. renal function, liver function, platelets or weight) may be required on an individual patient basis on the advice of the specialist. Anti-cancer therapy may cause fluctuations in platelets, liver function and or renal function which may influence dose and choice of anticoagulation. Many cancer patients may also experience significant fluctuations in their weight which again may influence dose and choice of anticoagulation. In all cases of uncertainty – refer to specialist team for advice. As a general rule for patients receiving systemic anti-cancer therapy, patients should have their weight, FBC, U+Es and LFTs checked monthly.

Drug Interactions

See SPC/BNF for common interactions.

There is little information regarding the effect of DOACs on anticancer drugs. None of the DOACs are inhibitors or inducers of CYP3A4 (cytochrome P450 3A4), P-gp (P-glycoprotein) or BRCP (Breast Cancer Resistance Protein). Consequently, they are unlikely to affect the pharmacokinetics of other substrates including anti-cancer drugs.

There is limited evidence on the effect of anti-cancer agents on DOACs. Information is largely theoretical. Potential interactions may occur particularly with drugs which are either inhibitors or inducers of CYP3A4 and/or p-gp. The following anti-cancer agents may theoretically affect plasma concentrations of DOACs and LMWH may be more appropriate. Please note that this is not an exhaustive list and use of a DOAC is not necessarily contraindicated.

Inhibitors (enhance anticoagulant effects, increase risk of bleeding)

- Imatinib; Crizotinib; Vemurafenib; Bicalutamide; Encorafenib

Inducers (reduce anticoagulant effects, increase risk of thrombosis)

- Enzalutamide; Bexarotene; Paclitaxel (not docetaxel); Encorafenib; Dabrafenib

Cost

At current prices one year's treatment with DOACs will be expected to be in the range £588-638. (For comparison, LMWH treatment is expected to be in the range £1416-3408 with additional consumable costs). Reference Regional Drug and Therapeutic Centre Cost Comparison Charts Jan 2020.

References

- Agnelli, G., Becattini, C., Meyer, G., Muñoz, A., Huisman, M.V., Connors, J.M., Cohen, A., Bauersachs, R., Brenner, B., Torbicki, A. and Sueiro, M.R., 2020. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. New England Journal of Medicine.
- Dranitsaris, G., Vincent, M. and Crowther, M., 2006. Dalteparin versus Warfarin for the Prevention of Recurrent Venous Thromboembolic Events in Cancer Patients. Pharmacoeconomics, 24(6), pp.593-607.
- Karimi, M. and Cohan, N., 2010. Cancer-associated thrombosis. The open cardiovascular medicine journal, 4, p.78.
- Marshall, A., Levine, M., Hill, C., Hale, D., Thirlwall, J., Wilkie, V., French, K., Kakkar, A., Lokare, A., Maraveyas, A. and Chapman, O., 2020. Treatment of cancer-associated venous thromboembolism: 12-month outcomes of the placebo versus rivaroxaban randomization of the SELECT-D Trial (SELECT-D: 12m). Journal of Thrombosis and Haemostasis.
- Mulder, F.I., van Es, N., Kraaijpoel, N., Di Nisio, M., Carrier, M., Duggal, A., Gaddh, M., Garcia, D., Grosso, M.A., Kakkar, A.K. and Mercuri, M.F., 2020. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: Results from the Hokusai VTE Cancer study. Thrombosis research, 185, pp.13-19.
- National Institute for Clinical Excellence, 2020. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Nice guideline (CG158).
- Electronic Medicines Compendium (EMC). Available at: www.medicines.org.uk

Document details

Document prepared by Nathan Hutchinson-Jones (Lead Pharmacist for Thrombosis and Anticoagulation, RUH Bath) on the 11/05/2020. Next review due May 2022.