Dalteparin (Fragmin®) (Amber TLS)

RUH Shared Care Guidelines: For the treatment of cancer associated thrombosis

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of **dalteparin 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. Discuss the benefits and side effects of treatment with the patient. To ensure patient has a basic understanding of what risks and benefits are associated with dalteparin therapy, to provide a patient information leaflet and to inform the patient of what action to take in the event of adverse effects (particularly any unexplained bleeding).
2. Confirm the patient's understanding, and consent to treatment and to inform the patient of the need for blood monitoring.
3. Undertake baseline monitoring (detailed below).
4. Discontinue any drugs affecting haemostasis, if deemed appropriate (e.g. NSAIDs, antiplatelets).
5. Initiate treatment with dalteparin and provide the first 30 days of treatment and to inform the patient of the arrangements for obtaining further prescriptions and provide at least 30 days' supply. (Although it is standard for 28 days treatment to be provided, 30 days is more appropriate in this instance as dalteparin is packed in multiples of 5 syringes).
6. Instruct the patient or carer on administration (or arrange for GP practice nurse or district nurse (where patient house bound) to be involved)
7. Monitor for heparin-induced thrombocytopenia (HIT) or hyperkalaemia. The patient should undergo repeat monitoring within the first 3 weeks of treatment. It is the responsibility of the initiating physician to ensure that the patient has received clear advice and that any discrepancies are actioned appropriately.
8. 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.
9. Review the patient's condition and monitor response to treatment regularly where indicated.
10. Give advice to the GP on when to stop treatment.
11. Report adverse events to the MHRA.
12. Ensure that clear backup arrangements exist for GPs to obtain advice and support.
13. Initiating clinician to keep patient under clinical review, assessing need for ongoing dalteparin treatment at six months.
14. Where the risk/benefit to the patient is considered to favour continuation beyond the licensed six-month duration then, with the patient's acceptance, further written consent should be obtained from the GP for the continued off label prescribing.
15. Ensure the patient has a sharps bin to dispose of used syringes.

General Practitioner responsibilities
1. Reply to the request for shared care as soon as practicable. 2. Monitor and prescribe dalteparin in collaboration with the specialist and follow these guidelines. 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. Whenever practicable, to reaffirm with the patient the importance of reporting any unexplained bleeding. 6. Monitor for hyperkalaemia in those patients at higher risk of raised plasma-potassium concentrations. 7. To give a timely response to any further specialist request to continue prescribing dalteparin beyond the licensed six-month duration. Clinicians should use their discretion to avoid any interruptions in treatment. 8. Discontinuation of treatment if patient is experiencing severe side effects and specialist advice is not immediately available. 9. 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. To attend hospital and GP clinic appointments. Failure to attend will result in medication being stopped on specialist advice. 4. To report adverse effects to their specialist or GP (particularly any unexplained bleeding). 5. To dispose of syringes safely in sharps bin.

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	Medicines 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

This medicine is indicated for:

- Treatment of cancer associated thrombosis (CAT) (deep vein thrombosis (DVT) and pulmonary embolism (PE)) in patients with solid tumors for up to 6 months. Use beyond 6 months or in patients with haematological malignancy/ other type of thrombotic complication are off label.

Treatment aims (Therapeutic plan)

- Dalteparin is currently the only licensed LMWH for CAT and then only for a six month period. Dalteparin cannot be used interchangeably with other LMWHs. Dalteparin is currently the LMWH of choice across BSW.

Treatment Schedule (including dosage and administration)
NB: Patients with cancer often experience dramatic changes in weight and this should be monitored to ensure the correct dose of dalteparin is prescribed.

Month 1
Administer dalteparin 200 units/kg total body weight subcutaneously (SC) once daily for the first 30 days of treatment (see table below)

Body weight (kg)	Dose (units)
< 46	7,500
46 – 56	10,000
57 – 68	12,500
69 – 82	15,000
≥ 83	18,000

Dalteparin should not be administered by the intramuscular route. The total daily dose should not routinely exceed 18,000 units daily. For patients > 120 kg higher doses may be used on the discretion of the specialist (unlicensed dose).

Months 2 – 6
Administer dalteparin 150 units/kg SC once daily (see table below)

Body weight (kg)	Dose (units)
< 56	7,500
57 – 68	10,000
69 – 82	12,500
83 – 98	15,000
≥ 99	18,000

In some patient groups it may be appropriate to continue with the full therapeutic 1 month dose of dalteparin beyond the first month on the advice of a specialist (off label). For example:

- Patients with a PICC line associated DVT
- Patients with an additional indication for anticoagulation (e.g. atrial fibrillation)
- Patients with pancreatic cancer
- Patients with recurrent VTE

It is at the discretion of the GP to decide on whether they are happy to continue supply on the advice of a specialist for 'off-label' use.

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.

Some patients initially started on treatment with dalteparin may be able to be changed to a direct oral anticoagulant (DOAC) on the advice of a specialist. DOACs for the treatment CAT is also part of a shared care agreement with primary care (See link here).

Renal failure
Therapeutic LMWH should be used with caution in patients with renal impairment and dose reduction or anti-Xa monitoring may be indicated in patients with a **GFR < 30ml/min**.

Extended anticoagulation beyond 6 months
Recommended duration of treatment is six months. Relevance of continuing treatment beyond this period will be evaluated according to individual risk/benefit ratio, taking into account particularly the progression of cancer. No data is available with dalteparin beyond six months of treatment in the CLOT study. In practice an individual specialist /clinician may choose to extend the duration beyond six months, however use is off-label. It is at the discretion of the GP to decide on whether they are happy to continue supply beyond 6 months on the advice of a specialist.

Contra-indications and precautions for use

- Patients with the following conditions are excluded from this protocol:

- Known or suspected hypersensitivity to dalteparin or other LMWHs and/or heparins.
- History of immunologically mediated Heparin Induced Thrombocytopenia.
- Renal impairment (calculated creatinine clearance < 30ml/min).
- Significant hepatic impairment.
- Active gastric/duodenal ulceration or oesophageal varices.
- Haemophilia and other inherited/major bleeding disorders or any unusual susceptibility to bleeding or haemorrhagic pericardial/ pleural effusion.
- Thrombocytopenia with platelets < 50.
- Recent (within three months) cerebral haemorrhage (stroke due to systemic emboli excepted).
- Severe hypertension.
- Recent neurosurgery or eye/ear surgery and injuries to the central nervous system, eyes and ears
- Subacute endocarditis.
- Children under 16 years.
- Low body weight (< 40kg at time of venous thromboembolic event).
- Body weight >90 kg.
- Pregnancy.
- In patients receiving dalteparin for treatment (rather than prophylaxis), local and/or regional anaesthesia in elective surgical procedures is contra-indicated.

Side effects

Clinical condition (reported frequency)	**Proposed management**
Major haemorrhage (<1%)	Stop dalteparin and seek urgent advice
Skin necrosis at the site of injection (<1%)	Stop dalteparin and seek urgent advice
Cutaneous or systemic allergic reaction (>1% - <10%)	Stop dalteparin and seek urgent advice
Pain, haematoma and mild local irritation at injection site (>1% - <10%)	Continue dalteparin, may be self-limiting, and seek advice if needed.

Please see the BNF and SPC for a comprehensive list.

Other side effects:

- Long term treatment with heparin has been associated with an increased risk of osteoporosis, although this has not been specifically observed with dalteparin.
- Heparins can increase the risk of hyperkalaemia. Clinically relevant hyperkalaemia may occur in patients with chronic renal failure or diabetes.

Patients should report any bleeding immediately. All serious adverse events should be reported to the MHRA.

Monitoring

Baseline monitoring: To be undertaken by the specialist.

- FBC; U+Es; LFTS; Clotting screen; Weight

Ongoing monitoring:

Parameter	**Frequency of monitoring**	**Action (adjustment and referral back to hospital)**
FBC	Monthly	Platelets < 50 or drop in count of more than 50% - discuss with specialist/ Haematology as soon as possible.
U & E	Monthly (*if high risk of hyperkalaemia i.e. those with diabetes mellitus, chronic renal failure, acidosis, raised potassium concentrations or those taking potassium-sparing drugs / potassium supplements*)	K > 5.5mmol/L Repeat the U & E test and seek specialist/ Haematology advice if K still > 5.5mmol/L
Weight	Monthly	Adjust dose of dalteparin as per dosing schedule if needed. Discuss with specialist as needed.

Other specific monitoring / monitoring parameters may be requested by the specialist depending on the individual patient circumstances.

Drug Interactions
See SPC/BNF for common interactions.

Drugs affecting haemostasis such as aspirin, dipyridamole, NSAIDS and clopidogrel should be discontinued prior to dalteparin therapy unless their use is essential.

Dalteparin may increase the risk of hyperkalaemia in patients on potassium-sparing drugs (e.g. ACE inhibitors).

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

References
1. National Institute for Clinical Excellence, 2020. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Nice guideline (CG158).
2. Dalteparin. Pfizer. Summary of product characteristics (SPC). www.medicines.org.uk Last updated: 17 Apr 2020
3. Lee, Agnes YY, et al. "Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer." New England journal of medicine 349.2 (2003): 146-153.

Document details
Document reviewed by Nathan Hutchinson-Jones (Lead Pharmacist for Thrombosis and Anticoagulation, RUH Bath) on the 28/05/2020. Next review due May 2022.