SHARED CARE GUIDELINES FOR PRESCRIBING LOW MOLECULAR WEIGHT HEPARINS FOR TREATMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS

INDICATION

Dalteparin and enoxaparin are low molecular weight heparins (LMWH) that have been demonstrated as superior to warfarin for treatment of thromboembolic disease in cancer patients, in terms of risk of further thromboembolic events and complications. Cancer cells can produce Tissue Factor hence the increased risk of a venous thrombosis occurring. LMWH are the only anticoagulants that cause a release of an inhibitor to Tissue factor from the endothelial cells hence their superiority over oral anticoagulation therapy. No studies have been completed comparing the effects of LMWH to DOACs. Dalteparin is licensed for cancer-related VTE.

This shared care guideline covers the prescribing of dalteparin or enoxaparin for venous thromboembolism treatment in patients with active cancer (treatment ongoing, within 6 months or palliative cases). For patients without active cancer; anticoagulation should be with warfarin as in other medical patients.

This shared care guideline does not cover the prophylaxis of VTE in cancer patients, which remains the responsibility of the appropriate secondary care specialist.

This approach has been endorsed by NICE in Clinical Guideline 144; Venous Thromboembolic Diseases: The management of venous thromboembolic diseases and the role of thrombophilia testing.

Patients should be trained and encouraged to self-administer LMWH.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of LMWH can be 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.

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

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed in each individual case
- Patients should only be transferred to shared care once they are no longer routinely attending for treatment at the specialist service (no longer being seen on a monthly basis).
- Prescribing responsibility will only be transferred when the patient's condition is stable or predictable.
- The Consultant will communicate to the GP the reason for choice of LMWH over warfarin, the specific indication for use and intended duration of treatment.

Specialist Responsibilities	
1.	Perform baseline assessment and monitoring including the patient's weight in order to calculate the dose.
2.	To initiate and stabilise the patient on treatment with LMWH, supplying at least the first 28 days treatment or until patients are no longer attending for treatment at the specialist service on at least a monthly basis.
3.	To supervise and prescribe LMWH for the duration of chemotherapy administration
4.	To ask the GP whether he or she is willing to participate in shared care. Requests to GPs should be made in writing and must include appropriate information to allow an informed decision to be made.
5.	On agreement from the GP, to provide the GP with appropriate information, including LMWH dose and renal function along with relevant clinical and physical assessment information to support the transfer of clinical responsibility. If, at the consultant's discretion / Trust policy, platelet monitoring is considered necessary after transfer to primary care, this should be made explicit to the GP.
6.	To communicate promptly with the GP when treatment is changed, stopped or adjusted and to communicate changes in response to treatment or the condition itself.
7.	Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
8.	Ensure that clear backup arrangements exist for GPs to obtain advice and support.
9.	To ensure the patient has sufficient supply of medication until such time as is appropriate for the GP to assume prescribing responsibility. This may include times to cover initial transfer of responsibility and/or after 3 month reviews
10.	To ensure the patient/ carer has given informed consent to their treatment.
11.	To provide the patient, carers/parents and teachers with comprehensive advice and information about the expected side effects and their management.
12.	To arrange for the patient to be trained to self-administer the LMWH. The specialist should check that the patient is able and willing to comply with treatment. Advise the patient to report if they have any unexplained bruising.
13.	To be available for advice if the patient's condition changes, ensuring that procedures are in place for the rapid re-referral of the patient by the GP.
14.	To liaise with the GP on any suggested changes in prescribed therapy and to stop treatment where appropriate.
15.	To review the patient in an outpatient appointment at least every 3 months (based on clinical need) and make suitable arrangements for long-term anticoagulation if patients are to continue treatment after 6 months of LMWH.
16.	Report adverse events to the MHRA via the Yellow Card system

General Practitioner Responsibilities	
1.	Reply to the request for shared care as soon as practicable.
2.	Where appropriate, to prescribe LMWH at doses agreed with the specialist, when the patient's condition is stabilised. Where explicitly requested by the consultant to undertake platelet monitoring.
3.	To refer back to the consultant if a change in the patient's clinical condition suggests that LMWH is no longer appropriate.
4.	If comorbid conditions / medications instituted that may substantially affect renal function, to monitor biochemistry and refer back to consultant for advice if CrCl< 45ml/min/1.73m^2 (dosing adjustments are indicated if CrCl < 30ml/min). Patients with renal impairment should have their dose determined and stabilised in secondary care, with factor Xa monitoring if appropriate, prior to shared care recommencing.

5.	As part of the review process check to ensure that the patient is able to comply and is concordant with treatment.
6.	Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
7.	Report adverse events to the specialist and via the Yellow Card system. Advise the patient to report if they have any unexplained bruising.

Patient's role (or that of carer)	
1.	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2.	Attend appropriate consultant and GP appointments
3.	Be prepared to learn how to self-administer the injection.
4.	Share any concerns in relation to treatment with LMWH.
5.	Use written and other information on the medication.
6.	Seek help urgently if it is suspected that LMWH is causing side effects, if they have any unexplained bruising, or if the patient is otherwise unwell.

SUPPORTING INFORMATION

DALTEPARIN

Dosage and Administration

Dosage will be communicated from the specialist to the GP as part of the shared care process, bearing in mind that acute Trusts may use dose-banding based on the patient's weight for LMWH and considering renal function.

Dalteparin is administered by once daily subcutaneous injection based on patient's weight. The dose in venous thromboembolism in patients with active and or metastatic cancer is 200 IU/kg total body weight subcutaneously (SC) once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily. For months 2-6 dalteparin should be administered at a dose of approximately 150 IU/kg, subcutaneously, once daily using fixed dose syringes

Contraindications

Contraindications included in the current Summary of Product Characteristics include:

- Hypersensitivity to either dalteparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins
- Known bleeding disorders, e.g. haemophilia
- Thrombocytopenia with platelet count < 50 x 10^9/L
- History of heparin-induced thrombocytopenia (HIT)
- Peptic ulcer
- Recent cerebral haemorrhage
- Major / life threatening bleeding
- Severe hypertension – Systolic BP > 230 mmHg + Diastolic BP > 120mm Hg
- Severe liver disease with oesophageal varices
- Major trauma
- Recent eye, brain, spinal cord surgery
- Acute bacterial endocarditis

Special Warnings

Dalteparin injection, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as: impaired haemostasis, history of peptic ulcer, recent ischaemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy,

recent neuro- or ophthalmologic surgery.
Caution should be exerted with concomitant use of drugs that increase bleeding, liver disease, recent surgery, pre-existing diseases or concomitant use of drugs that cause hyperkalaemia and osteoporosis

In patients with renal impairment, there is an increase in dalteparin exposure which increases the risk of bleeding. Since dalteparin exposure is significantly increased in patients with severe renal impairment dosage adjustments are recommended in therapeutic dosage for CrCl<30ml/min.

Routine monitoring of anticoagulant effect is not required except in special circumstances below-

- Patients having treatment doses for more than 10 days and who have a creatinine clearance between 20ml/min and 30ml/min
- Obesity (BMI > 30kg/m^2)
  Pregnancy
- Those at increased risk of bleeding

The requirement for routine monitoring will be communicated to the GP.

Side Effects

Although dalteparin is generally well tolerated, the following effects may occur:

- The risk of heparin-induced thrombocytopenia is lower with the LMWHs compared to unfractionated heparin; however clinicians should still be alert to this condition. Routine platelet count monitoring is no longer recommended.
- If renal impairment (Creatinine Clearance <30ml/min) occurs as a consequence of comorbid conditions then LMWH may need to be stopped or dose reduced and consultant advice should be sought.
- Hyperkalaemia may occur but is rarely clinically relevant; if new medication or comorbid conditions predisposing to hyperkalaemia occur then potassium levels should be monitored.
- Osteoporosis may be accelerated by LMWH and for patients with good prognosis (e.g. breast/prostate cancer) and other risk factors for osteoporosis active management of this should be considered. Drug management of osteoporosis should be started on the recommendation of the Oncologist.

Drug Interactions

It is recommended that agents which affect haemostasis should be discontinued prior to dalteparin therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and anticoagulants. If the combination cannot be avoided, dalteparin should be used with careful clinical and laboratory monitoring.

Drug costs

Strength	Cost for 30 days treatment (Daily injection)
Dalteparin Sodium 7,500units/ 0.3ml solution for injection pre-filled Syringes	**£127.02**
Dalteparin Sodium 10,000units/ 0.4ml solution for injection pre-filled Syringes	**£169.38**
Dalteparin Sodium 12,500units/ 0.5ml solution for injection pre-filled Syringes	**£211.74**
Dalteparin Sodium 15,000units/ 0.6ml solution for injection pre-filled Syringes	**£254.04**

Dalteparin Sodium 18,000units/ 0.72ml solution for injection pre-filled Syringes	**£304.92**

Prices based on June 2017 Drug Tariff

ENOXAPARIN

Dosage and Administration

Dosage will be communicated from the specialist to the GP as part of the shared care process, bearing in mind that acute Trusts may use dose-banding based on the patient's weight for LMWH and considering renal function.

Enoxaparin is administered by daily subcutaneous injection. The dose in venous thromboembolism in patients with active and or metastatic cancer is 1.5mg/kg daily for one month, then 1mg/kg daily. Anticoagulation with enoxaparin should be continued for a total of 6 months. The patient should then be reviewed by the specialist and relevance of continuing treatment beyond 6 months evaluated according to individual risk/benefit ratio.

Contraindications

Contraindications included in the current Summary of Product Characteristics include:

- Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins
- Acute bacterial endocarditis
- Active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke, thrombocytopenia in patients with a positive in- vitro aggregation test in the presence of enoxaparin
- Active gastric or duodenal ulceration

Special Warnings

Enoxaparin is best avoided in patients with a history of heparin-induced thrombocytopenia with or without thrombosis.

Enoxaparin injection, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as: impaired haemostasis, history of peptic ulcer, recent ischaemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy, recent neuro- or ophthalmologic surgery.

In patients with renal impairment, there is an increase in enoxaparin exposure which increases the risk of bleeding. Since enoxaparin exposure is significantly increased in patients with significant renal impairment (creatinine clearance < 30 ml/min) dosage adjustments are recommended.

In low-weight women (< 45 kg) and low-weight men (< 57 kg), an increase in enoxaparin exposure has been observed within the prophylactic dosage ranges (non-weight adjusted), which may lead to a higher risk of bleeding and careful monitoring is required.

Side Effects

Although enoxaparin is generally well tolerated, the following effects may occur:

- The risk of heparin-induced thrombocytopenia is lower with the LMWHs compared to unfractionated heparin; however clinicians should still be alert to this condition. Routine platelet count monitoring is no longer recommended.

- If renal impairment (creatinine clearance <30ml/min) occurs as a consequence of comorbid conditions then LMWH may need to be stopped or dose reduced and consultant advice should be sought.
- Hyperkalaemia may occur but is rarely clinically relevant; if new medication or comorbid conditions predisposing to hyperkalaemia occur then potassium levels should be monitored.
- Osteoporosis may be accelerated by LMWH and for patients with good prognosis (e.g. breast/prostate cancer) and other risk factors for osteoporosis active management of this should be considered. Drug management of osteoporosis should be started on the recommendation of the Oncologist.

Drug Interactions

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and anticoagulants. If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug cost:

Strength	Cost for 30 days treatment (Daily injection)
Enoxaparin 60mg/0.6ml solution for injection pre-filled syringes	**£117.78**
Enoxaparin 80mg/0.8ml solution for injection pre-filled syringes	**£165.39**
Enoxaparin 100mg/1ml solution for injection pre-filled syringes	**£216.90**
Enoxaparin 120mg/0.8ml solution for injection pre-filled syringes	**£263.79**
Enoxaparin 150mg/1ml solution for injection pre-filled syringes	**£299.73**

Prices based on June 2017 Drug Tariff

COMMUNICATION AND SUPPORT

PHT Hospital Switchboard Tel: 01202 665511	RBCH Hospital Switchboard Tel:01202 303626	DCH Hospital Switchboard Tel:01305 251150
Haematologists		
Dr F Jack Dr R Maddams Dr R Jayaprakash Dr L Fraser Dr D Furby	Dr J Chacko Dr R Hall Dr H McCarthy Dr J Mainwaring Dr S Killick Dr R Walewska	Dr D Hofer Dr A Morris
Oncologists (Working across sites)		
Dr M Bayne Dr T Hickish Dr T Geldart Dr M Flubacher	Dr J Brady Dr S Brock Dr P Crellin	Dr J Davies Dr A Chakrabarti
Summary of Product Characteristics for dalteparin and enoxaparin accessible via www.medicines.org.uk **Medicines Information**: RBCH Tel 01202 704098 / PHT Tel 01202 442127 / DCH Tel 01305 255171 **Anticoagulant Clinics:** RBCH Tel 01202 704781 / PHT Tel 01202 448391 / DCH Tel 01305 814007		

References

1. Summary of product characteristics (SPC) for Fragmin last updated 19th May 2016, accessed June 2017
2. Summary of product characteristics (SPC) for (Clexane®) last updated 09/06/2017, accessed June 2017

Written By	Dorset Cancer Network August 2012
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