SHARED CARE GUIDELINE

Low Molecular Weight Heparins
Treatment and prophylaxis of thromboembolic disease in non-obstetric adult patients

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

INTRODUCTION – Indication and Licensing

Anticoagulation is used in the management of venous thromboembolism (VTE), stroke prevention in AF and as antithrombotic therapy in patients with valve replacement. In instances where oral anticoagulation is not an option, low molecular weight heparin (LMWH) is used.

This shared care guideline (SCG) is written for all health care professionals involved in the prescribing, dispensing or administration of LMWH, namely enoxaparin and dalteparin and aims to provide sufficient information to ensure the LMWH is used safely and appropriately in primary care under shared care arrangements. This SCG aims to cover all licensed and unlicensed non-obstetric indications (treatment of VTE, stroke prevention in AF and as antithrombotic therapy in patients with valve replacement) in instances where oral anticoagulation is not an option. It is applicable to all patients who are to receive a LMWH and have been discharged from hospital, and are still under the routine care of a hospital specialist through outpatient follow up or who are being managed purely by a primary care clinician. It is not intended to guide management of inpatients in hospital or in a community hospital; the relevant Trust policies should be consulted in this instance. **Refer to separate shared care guidelines for maternity and obstetric patients.**

PATIENT PATHWAY

Clinical speciality/ indication	Treatment of venous thromboembolism (VTE), atrial fibrillation (AF), mechanical valve replacement in patients: • That are intolerant or have contraindications to oral anticoagulation • Where treatment failure has occurred with oral anticoagulation • That have cancer where drug-drug or drug-disease interactions with oral anticoagulation exist
Prescribing initiated by	Secondary care prescriber
Prescribing responsibility	Every patient initiated on LMWH will be seen in the thrombosis clinic within 4 weeks to assess and confirm the duration of therapy. At this review, the GP and patient will be informed of the decision to either continue therapy, change anticoagulation dose (if needed), stop therapy or re-assess mode of anticoagulation. • Hospital will supply 30 days of LMWH at initiation and a further 30 days after review. • Oncology/ thrombosis teams will advise when switching to oral anticoagulation would be appropriate, if applicable. ***Longer terms reviews:*** Thrombosis patients will be reviewed 6-12 monthly. AF/valve patients (largest group under oncology) will be seen at every oncology appointment/ chemo session which is variable.
Monitoring	**Monitoring undertaken by specialist before requesting shared care** • Full blood count (FBC) *N.B. Before transfer of care; platelet count should be stable (i.e. at least 2 stable FBC results no more than 6 weeks apart available before transfer of care)* • Clotting screen • Urea and electrolytes • Liver Function Tests

	Ongoing monitoring to be undertaken by GP after 8 weeks
	• Monitor U&Es, full blood count, liver function tests, weight:
	  • At least annually if CrCl >60ml/min
	  • 6 monthly review if CrCl 30-60ml/min and/or aged >75 years and/or frail
	• Check for side effects/ bleeding issues and patient adherence to therapy at each routine appointment.
	• Any additional as advised by specialist

Duration of treatment	**VTE treatment:** variable dependent on provoking factors. Duration will be communicated clearly in the letter requesting shared care.
	
	AF and valves: lifelong or until patient can be switched to oral anticoagulation (e.g. post chemo)
	
	Stopping Criteria
	• Active Significant bleeding
	• Symptomatic hyperkalaemia
	• Skin necrosis
	• Any clinically significant adverse effect
	• Thrombocytopenia
	  • ***Stopping threshold:*** platelet count <50 x10^9/L)
	  • ***Escalation threshold to secondary care:*** platelet count <100 x10^9/L

Key safety notice	Enoxaparin is a biological medicine where biosimilars are available. Therefore enoxaparin **must be prescribed by brand name** and the brand name specified on the prescription should be dispensed in order to avoid inadvertent switching (this will be communicated at the point of initiation).

DOSE AND ADMINISTRATION

Enoxaparin and dalteparin are the main LMWHs to be initiated by Homerton University Hospital, if another LMWH is deemed appropriate for the patient then the specialist commencing the medication will ensure that the relevant prescribing information is clearly specified in a clinic letter.

N.B. There are currently three enoxaparin biosimilar products available: Inhixa®, Arovi® and Enoxaparin Becat®, with Clexane® being the original biologic medicine. **MHRA recommends that when prescribing biological products, it is good practice to use the brand name to ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed or administered.**

VTE treatment

- Enoxaparin dose subcutaneously when CrCl >30 ml/min:
  - 1.5 mg/kg once daily in patients who do not meet the criteria for 1 mg/kg twice daily dosing (refer to Appendix 1 for dose banding)
  - 1 mg/kg twice daily for one of the following:
    - Patient weight >100 kg
    - Have recurrent or extension of thrombosis despite once daily LMWH
    - Have a very high risk of thrombosis recurrence or extension

- Enoxaparin dose subcutaneously when CrCl 15-30 ml/min: 1 mg/kg once daily
- If CrCl <15 ml/min: Dalteparin is the LMWH of choice – 133 units/kg once daily subcutaneously (refer to Appendix 2 for pre filled syringe size)

AF and mechanical valve replacement: these are unlicensed indications and therefore cardiac and cardiothoracic teams respectively advise on dose based on individual factors (enoxaparin dose range: 40 mg daily to 1 mg/kg twice daily)

Patients/carers will be taught how to self-administer/administer the LMWH. The hospital team will provide training on the administration of injections and provide initial sharps bin for the safe disposal of the syringes. If the patient is unable to self-administer, secondary care the patient will be referred to the community district nurse team and the GP notified accordingly.

CAUTIONS AND CONTRAINDICATIONS

Absolute Contraindications

- Active clinically significant bleeding and conditions with a high risk of haemorrhage
- Hypersensitivity to active ingredients
- New diagnosis of heparin-induced thrombocytopenia (HIT) or history of HIT within the past 100 days or in the presence of circulating antibodies

Relative Contraindications (under the haematology team's guidance)

- Hypersensitivity to heparins
- Hepatic impairment - liver disease with coagulopathy/varices
  - Acute bacterial endocarditis
- Known bleeding disorder (acquired or inherited), such as haemophilia and other haemorrhagic diseases
- Thrombocytopenia with platelets <50 x10^9/L
- Peptic ulcer disease (PUD) and/or oesophageal varices
- Recent cerebral haemorrhage or acute cerebral infarct (<3months – unless advised by stroke/neurology specialist)
- Severe and or uncontrolled hypertension:
  - Systolic blood pressure >200 mmHg and/or
  - Diastolic blood pressure >120 mmHg
- Baseline APTT of >31seconds, INR >1.3, or active bleed
- Major trauma or recent neurosurgery or eye surgery
- Spinal or epidural anaesthesia
- Past history of HIT
- Severe renal failure (CrCl < 15 ml/min) - including patients on dialysis.
- Impending miscarriage or abortion
- Prophylactic doses are not required if receiving therapeutic anticoagulation

For complete list of contraindications and cautions, please refer to the SPC: https://www.medicines.org.uk/emc

INTERACTIONS

Drugs affecting haemostasis (e.g. antiplatelets, anticoagulants, NSAIDs, systemic glucocorticoids, thrombolytics) should be discontinued before LMWH is initiated unless their use is essential. If the combination cannot be avoided, LMWH should be used with careful clinical and laboratory monitoring.

For complete list of drug interactions, please refer to the SPC: https://www.medicines.org.uk/emc

MONITORING STANDARDS FOR MEDICATION AT THE ACUTE NHS TRUST

Hospital specialist

It is the responsibility of the secondary care team to provide the following information:

- Initiate treatment and prescribe until the GP can make provisions for shared care. A letter to the GP requesting shared care for the patient will be sent. After review by the anticoagulation clinic the patient will be prescribed a further 30 days to allow for shared care agreement to be actioned.
- Drug name, dose, frequency, indication, expected duration of treatment, follow up date in secondary care if applicable and monitoring parameters and frequency of monitoring should be provided to the GP
- The following baseline parameters should be provided to the GP:
  - Full blood count (FBC)
  - Clotting screen (APTT and PT)

- Urea and electrolytes (U&Es)
- Liver function tests (LFTs)
- Weight (in kilograms

- In addition to this, specific patient information must be provided and included in the hospital discharge letter to enable the GP to safely continue prescribing anticoagulation (after the shared care agreement is signed). This will be as follows:
  - Drug name, dose, frequency; brand name (where there are multiple brands available)
  - Indication for treatment
  - Duration, where known
  - Patient weight
  - Dose
  - Dosing regimen per weight (i.e. X mg/kg or X units/kg)
  - Renal function
  - Follow up date in secondary care where applicable

- A rare complication of LMWH use is HIT which usually presents as a progressive fall in platelet counts; either below 100 x 10^9/L or by greater that 50% of the pre-heparin level - the patient's platelet count should be stable prior to transfer of care

Secondary care team to:
- If required, co-ordinate district nurse administration
- Evaluate any reported adverse effects referred by GP or patient and relay changes in management of patient to GP/secondary clinician in writing

KEY ADVERSE EFFECTS & ACTIONS

If the patient reports one of the adverse events listed in table below, the hospital team should be informed

Adverse effects	**Symptoms/signs** *(specify what would prompt action)*	**Actions (***what action should the GP take if identified in primary care)*
Skin rashes/minor bruising	Occasionally this can occur at the site of injection. Systematic allergic reactions have been reported rarely.	If problematic seek advice from a haematologist.
Skin necrosis	The first symptoms are pain and redness in the affected area. Progression can lead to lesions which become petechial, then hard and purpuric. This is a rare adverse effect.	Withdraw treatment and seek a haematologist's advice.
Thrombocytopenia	Platelet count <100x10^9/l OR drop of >50% from baseline platelet count.	Contact a haematologist for advice.
Heparin-induced thrombocytopenia (HIT)	Immune-mediated heparin-induced thrombocytopenia (type II) largely manifests within 5 to 14 days of receiving the first dose. Furthermore, a rapid-onset form has been described in patients previously exposed to heparin. Immune-mediated heparin-induced thrombocytopenia (type II) may be associated with arterial and venous thrombosis. LMWH must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia.	Platelet count should be measured before the start of treatment and periodically thereafter because of the risk of immune-mediated heparin-induced thrombocytopenia (type II). LMWH must be discontinued in patients who develop immune-mediated heparin-induced thrombocytopenia (type II). Platelet counts will usually normalise within 2 to 4 weeks after withdrawal. Seek advice from a haematologist.

Haemorrhage	LMWHs have been shown to increase the risk of haemorrhage.	Action will vary depending on severity of haemorrhage-seek advice from haematology if necessary. For severe bleeding stop treatment and refer the patient to A&E.
Liver function tests	Raised transaminases. This is reversible after drug withdrawal.	Seek advice from a haematologist if transaminase level increase by more than 3-fold or if symptoms develop.
Hyperkalaemia	Symptomatic hyperkalaemia is unlikely to develop in the absence other risk factors. LMWHs can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium-sparing drugs.	Plasma potassium should be monitored regularly especially in patients at risk. Stop if symptomatic hyperkalaemia develops. Seek advice from a haematologist team regarding alternative treatment.

For complete list of side effects, please refer to the SPC: https://www.medicines.org.uk/emc

The SCG lists only the key information. Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information on cautions, contraindications, interactions and adverse effects.

PREGNANCY AND BREAST FEEDING

Enoxaparin and Dalteparin are considered safe to be used during pregnancy and breast feeding. LMWHs do **not** cross the placenta and have been used during all trimesters of pregnancy when clinically needed.

LMWH is excreted into breast milk in very small amounts. Because the drug would be inactivated in the GI tract, the risk to a nursing infant from ingestion of Enoxaparin or Dalteparin from milk appears to be negligible.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that the patient/carer understands their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations (if applicable) are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first month of treatment or until patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical and laboratory supervision of the patient by blood monitoring (if applicable) and routine clinic follow-up on a regular basis.

7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated (unless otherwise covered by letter e.g. from Clinical Nurse Specialist or Drug Monitoring Service).
8. Where the GP is out of area and is not performing the phlebotomy, the blood test form/EPR request MUST specify that blood results are also copied to the GP. Specialist team to check with pathology IT if unsure on how to do this.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP.
11. Inform GP of patients who do not attend clinic appointments.
12. Ensure that backup advice is available at all times.

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA / CHM, where appropriate.
5. Help in monitoring the progression of disease.
6. Prescribe the drug treatment as described.

City and Hackney Medicines Management Team

1. To provide feedback to acute trusts via Joint Prescribing Group.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support acute trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease
5. Take/ administer the medication as prescribed.
6. Undertake any monitoring as requested by the GP and/or specialist.

Costs

Drug Product	Cost in primary care
Clexane® (enoxaparin reference brand) Inhixa® (enoxaparin biosimilar)	60mg/0.6ml x 10 pre-filled syringes = £39.26 80mg/0.8ml x 10 pre-filled syringes = £53.13 100mg/1ml x 10 pre-filled syringes = £72.30 120mg/0.8ml x 10 pre-filled syringes = £87.93 150mg/1ml x 10 pre-filled syringes = £99.91
Arovi® (enoxaparin biosimilar)	60mg/0.6ml x 10 pre-filled syringes = £29.45 80mg/0.8ml x 10 pre-filled syringes = £41.35 100mg/1ml x 10 pre-filled syringes = £54.23 120mg/0.8ml x 10 pre-filled syringes = £65.95 150mg/1ml x 10 pre-filled syringes = £74.93
Fragmin® (dalteparin)	5,000units/0.2ml x 10 pre-filled syringes = £28.23 7,500units/0.3ml x 10 pre-filled syringes = £42.34 10,000units/1ml x 5 graduated pre-filled syringes = £28.23 10,000units/0.4ml x 5 pre-filled syringes = £28.23 12,500units/0.5ml x 5 pre-filled syringes = £35.29 15,000units/0.6ml x 5 pre-filled syringes = £42.34 18,000units/0.72ml x 5 pre-filled syringes = £50.82

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on (06/04/2021)]

Relevant contact details	
Consultant or Registrar on-call *via* switchboard	020 8510 5555
Clinical Nurse Specialist (if applicable)	0208 510 5764
Generic email for department (if applicable)	huh-tr.Antico@nhs.net
Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000
City and Hackney Medicines Management Team	0203 816 3224

References

- Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on (06/04/2021)]
- Summary of product characteristics for Clexane®, Arovi®, Inhixa®, Fragmin® <www.medicines.org.uk/emc>
- Shared care guideline for Low Molecular Weight Heparins (LMWH) for Treatment of thromboembolic disease - Barts Health NHS Trust
- Konstantinides, S.V. et al. (2019) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal, 41 (4), pp. 543-603.
- Oxford University Hospital: treatment of VTE in adults with dalteparin (Fragmin®) May 19. https://www.ouh.nhs.uk/services/referrals/specialist-medicine/documents/mil-v2- n2.PDF
- Homerton University Thrombosis Committee (2018) *Venous Thromboembolism Risk Assessment and prophylactic treatment (Version 4).*

APPENDIX 1

Enoxaparin treatment dose banding table

Body weight (Kg)	**Prescribed dose at 1.5mg/kg (mg)**	**Injection volume (ml)***	**Syringe size to be used**
40 - 43.9	60	0.6	60mg/0.6ml Syringe
44 – 50.9	70	0.7	80mg/0.8ml Syringe
51 – 56.9	80	0.8	80mg/0.8ml Syringe
57 - 63.9	90	0.9	100mg/1ml Syringe
64 – 68.9	100	1.0	100mg/1ml Syringe
69 – 73.9	105	0.7	120mg/0.8ml Syringe
74 – 84.9	120	0.8	120mg/0.8ml Syringe
85 - 94.9	135	0.9	150mg/1ml Syringe
95 – 103.9	150	1.0	150mg/1ml Syringe

APPENDIX 2

Dalteparin recommended pre filled syringe sizes for CrCL < 15

Body weight (Kg)	Dalteparin dose (units daily)
Under 46	5,000
46 - 56	6,500
57 – 68	8,500
69 – 82	10,000
83 – 98	12,500
99 – 112	15,000
113 – 137	18,000
138 – 165	10,000 *(BD)
> 166	12,500 * (BD)

Date SCG approved by Joint Prescribing Group (JPG): 10/2021 Review date: 10/2023