Shared Care Guideline for Low Molecular Weight Heparins (LMWH) for Treatment of thromboembolic disease

LMWHs: Enoxaparin and Tinzaparin

Executive Summary/ Critical Information

Indication	Route & Dose	Key aims of treatment in the long term	Monitoring undertaken by specialist before requesting shared care	Ongoing monitoring to be undertaken by GP	Duration of treatment	Stopping criteria	Follow up (weeks/months)
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	**<u>VTE treatment:</u>** **Enoxaparin** dose subcutaneously when CrCl >30ml/min: - 1.5mg per kg once daily in patients who do not meet the criteria for 1mg/kg twice daily dosing[1,2] (refer to Appendix 2 for dose banding) - 1mg per kg twice daily for one of the following: o Patient weight >100kg o Have recurrent or extension of thrombosis despite once-daily LMWH	Reduce the risk of VTE occurrence and recurrence. Reduced risk of stroke.	Full blood count (FBC) NOTE: Before transfer of care; platelet count should be stable (i.e. conduct at least 2 FBC before transfer of care) Clotting screen Urea and electrolytes Liver function tests	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	VTE treatment: Variable dependent on provoking factors. Duration will be communicated clearly in appendix at the point of Shared care agreement AF and valves – lifelong	Active significant bleeding Symptomatic hyperkalaemia Skin necrosis Any clinically significant adverse effect Thrombocytopenia ***Stopping threshold:*** platelet count <50 x10^9/L ***Escalation threshold to***	Every patient will be seen at thrombosis clinic within 3 months from VTE diagnosis 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),

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interactions with oral anticoagulation exist	○ Have a very high risk of thrombosis recurrence or extension **Tinzaparin** 175units/kg once daily subcutaneously when CrCl 20-30ml/min[3] **Tinzaparin** 125units/kg once daily subcutaneously when CrCl <20ml/min[3] **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: 40mg daily to 1mg/kg twice daily)		Weight in kilograms	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		***secondary care:*** platelet count <100 x10^9/L	stop therapy or re-assess if oral anticoagulation. Oncology/ thrombosis teams to advise when switching to oral anticoagulation would be appropriate, if applicable. ***Longer terms reviews:*** Thrombosis patients will be seen 6-12 monthly. AF/valve patients (largest group under oncology) will be seen at every oncology appointment/ chemo session which is variable.
Key Safety Notice (for instance: notification if prescribing must be brand specific or BNF cautionary and advisory warnings).							
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).							

1. Background

Venous thrombosis is a condition in which a thrombus forms in a vein. Blood flow through the affected vein can be limited by the clot, causing swelling and pain in the affected limb or area. Venous thrombosis most commonly occurs in the 'deep veins' in the legs, thighs, or pelvis and can sometimes affect the arms or other veins. This is known as a deep vein thrombosis (DVT). An embolism is created if a part or all of the blood clot in the deep vein breaks free and travels through the venous system. If the clot lodges in the lung a pulmonary embolism (PE) arises, which can be life threatening. DVT and PE are collectively known as venous thromboembolism (VTE).

This guideline is written for all health care professionals involved in the prescribing, dispensing or administration of LMWH namely enoxaparin and tinzaparin and aims to provide sufficient information to ensure the LMWH is used safely and appropriately in primary care under shared care arrangements. It aims to cover all indications (licensed and unlicensed) for the 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.

2. Important information

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[4].

3. Drug name, form, and licensed indications (unlicensed/off-label)

Refer to table on page 1.

4. Dose and Administration

Refer to table on page 1.

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 a sharps bin for the safe disposal of the syringes. If the patient is unable to self-administer the patient will be referred to the community district nurse team which will be organised by secondary care and the GP notified accordingly.

5. Contraindications/Cautions

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

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- 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
- Severe and or uncontrolled hypertension:
  - Systolic blood pressure >200mmHg and/or
  - Diastolic blood pressure >120mmHg
- 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 < 30ml/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.

6. Drug 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.

7. Process for Referral Back to Secondary Care

If the patient reports one of the adverse events listed in table below, the hospital Clinical Haematology team should be informed using contact details listed in section 9.

Adverse effects	Symptoms/signs	Actions
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	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

	associated with arterial and venous thrombosis. LMWH must be discontinued in all cases of immune-mediated heparin-induced thrombocytopenia.	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.

8. Monitoring and Responsibilities

a. Hospital specialist:

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

- Initiate treatment and prescribe until the GP formally agrees to share care. Send a letter to the GP requesting shared care for this patient – complete "Shared Care Guideline Prescribing Agreement' (Appendix 1).
- Supply a minimum of 30day of LMWH on discharge 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 applicable, e.g. biologics)
- Indication for treatment
- Duration, where known
- Patient weight
- Dose
- Dosing regimen per weight (i.e. Xmg/kg)
- Renal function or statement that patient is on dialysis for tinzaparin
- Follow up date in secondary care

Current Medication	Dose	Frequency	No. Days	Cont.	Pharm Verify	Pharmacy Comments
Enoxaparin (subcutaneous)	100mg	Daily	30 days	Yes	Yes	*NEW* Ind: DVT. (Patient weight 64kg, CrCl =19ml/min). Dose 1.5mg/kg. Patient has thrombosis clinic booked for 05/05/20 to review duration.

Example of information presented in a discharge letter:

From both settings above:

- A rare complication of LMWH 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, before transfer of care the patient's platelet count should be stable
- Offer clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up where secondary care is monitoring
- In an instance where LMWH is not prescribed in accordance to Trust guidelines, then clear guidance will be sent to the GP
- Ensure that the patient/carer is an informed recipient of the therapy and they understand their treatment regimen and any monitoring or follow up that is required. Issue patient information leaflets and provide training on administration and safe disposal of syringes
- Where appropriate, counsel the patient on contraception and what to do if pregnancy occurs
- If required, co-ordinate district nurse administration

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- Evaluate any reported adverse effects referred by GP or patient and relay changes in management of patient to GP in writing
- Where urgent action is required following tests the hospital team will telephone the patient and inform GP via verbal and written communication
- Inform GP, in writing, of clinic visits and actions taken for management of patient or if patient does not attend clinic appointments

b. General Practitioner:

- Reinforce the patient's understanding of 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
- Monitor patient's overall health and well-being
- Report any adverse events to the consultant, where appropriate
- Report any adverse events via the yellow card scheme, where appropriate
- Monitor the progression of disease as guided by secondary care
- Carry out monitoring as guided by secondary care
- Prescribe the drug treatment as described, adjusting for changes in body weight/renal function where appropriate

c. Patient or parent/carer:

- Ensure they have a clear understanding of their treatment and potential adverse effects
- Administer the medication as prescribed
- Report any adverse effects to GP/secondary care team
- Report any changes in disease symptoms to GP/secondary care team
- Alert GP/secondary care team of any changes of circumstance which could affect management of disease e.g. plans for pregnancy
- Attend all appointments for monitoring, as requested by the GP/secondary care team

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9. Contact Information

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Contact	*Telephone number / bleep*
Barts Health NHS Trust Consultant Haematologists	Telephone (via switchboard) 0203 416 5000 and ask for site & department OR Via advice and guidance
Royal London and St Bartholomew's	
Haematology SpR	Telephone 0203 416 5000 Bleep 1155 or via switchboard out of hours
Anticoagulation clinic (For Postcodes: E1, E2, E3, E14, EC1, EC2, EC3, EC4, WC1V, WC2A, N1)	020 3594 1885 OR Email: theanti.coagteam@nhs.net
Pharmacist	0203 465 6352
Newham University Hospital	
Haematology SpR	Telephone (via switchboard) bleep 4130/4247
Anticoagulation clinic (For Postcodes: E6, E7, E12, E13, E15, E16, E20)	020 7363 8730 OR Email: newhamanticoagteam@nhs.net/ BHNT.Newhamanticoagteam@nhs.net
Whipps Cross University Hospital	
Haematology SpR	Telephone (via switchboard) Bleep 2075/2076
Anticoagulation clinic (For Postcodes: E4, E10, E11, (parts of E6, E7, E12), E17, E18, IG1-10)	020 8535 4538 OR Email: wxanticoadmin@bartshealth.nhs.uk
Clinical Commissioning Group Medicines Optimisation Team	
Newham CCG	Telephone: 0203 688 2654 NEWCCG.medcinesmanagement@nhs.net
Tower Hamlets CCG	Telephone: 020 36882556 THCCG.medicinesoptimisation@nhs.net
Waltham Forest CCG	Telephone: 0203 688 2654 WFCCG.MedicinesOptimisation@nhs.net

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10. References

[1] 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.

[2] TECHDOW PHARMA LTD (2020) *Inhixa 4,000 IU (40 mg) in 0.4 mL solution for injection in pre-filled syringe*. [Online] Available from: https://www.medicines.org.uk/emc/product/784/smpc#.

[3] THE RENAL DRUG DATABASE (2017) *TINZAPARIN SODIUM (LMWH)*. [Online] Available from: https://renaldrugdatabase.com/monographs/tinzaparin-sodium-lmwh.

[4] UK MEDICINES INFORMATION (2017) *In Use Product Safety Assessment Report For Enoxaparin Biosimilars (Inhixa and Arovi)*
Available from: https://www.sps.nhs.uk/articles/in-use-product-safety-assessment-report-for-inhixa-enoxaparin-biosimilar/.

11. Document Management

Document ratification and history	
Produced by:	Anticoagulation and Thrombosis team
Approved by:	Barts Health Drugs and Therapeutics Committee (DTC) Waltham Forest and East London Medicines Optimisation and Commissioning Committee (WELMOCC)
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Appendix 1.

Shared Care Guideline: Prescribing Agreement	
Section A: To be completed by the hospital consultant initiating the treatment	
GP Practice Details: Name: Tel No: Email (nhs.net):	**Patient Details:** Name: DOB: NHS Number (10 digits):
Consultant Details: Consultant Name: Secretary Contact Details: Tel No: Email (nhs.net):	
Diagnosis: **Duration**:	**Drug Name (to be prescribed by GP):** **Dose:** **Frequency:**
I will review the patient in clinic in weeks / months (*Delete as appropriate)*.	

Dear

Your patient started treatment with the above drug for the above diagnosis on (insert date) and in my view; his/her condition is now stable.

The patient has given consent to treatment under a shared care prescribing agreement and has agreed to comply with instructions and follow up requirements.

I am requesting your agreement to sharing the care of this patient from (insert date) in accordance with the attached Shared Care Prescribing Guideline.

This patient was reviewed on (insert date). These are the results relevant for the drug and/or condition, as outlined in the shared care document:

Test	Baseline	Date

Please continue to monitor the patient as outlined in the shared care guidelines. Refer to the attached guidelines for monitoring criteria.

Other relevant information:

Consultant Signature:	Date:

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above [If returned via e-mail, use NHS.net email account ONLY]

Please sign and return your agreement to shared care within 14 days of receiving this request.

☐ Yes, I accept sharing care as per shared care prescribing guideline.

☐ No, I am not willing to undertake shared care for this patient for the following reason:

(Please give reason)

GP Name:	GP Signature:	Date:

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Appendix 2: 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	0.60	60mg/0.6ml Syringe
44 – 50.9	70	0.70	80mg/0.8ml Syringe
51 – 56.9	80	0.80	80mg/0.8ml Syringe
57 - 63.9	90	0.90	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

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