Shared Care Prescribing Information for Low Molecular Weight Heparin (LMWH)

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of the drug treatment and clinical indication listed in the table below can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If GPs are not confident to undertake these roles, then they are 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 if they are unable to do so.

Sharing of care assumes **communication** between the specialist, the GP and the patient. The intention to undertake share care should be 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 requiring treatment with Low Molecular Weight Heparin 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.

Generic Name	
"Low Molecular Weight Heparin" (LMWH)	
Generic Names (Proprietary / Brand Names) of available products	
Dalteparin sodium (*Fragmin*®) Enoxaparin (*Clexane*®) Tinzaparin (*Innohep*®)	
Date of last review by the TAG	**Due Date for Review**
September 2017	August 2022
Authors / organisations	
Developed by Dr Jennie Wimperis, Consultant in Haematology, Norfolk and Norwich University Hospital Foundation NHS Trust in consultation with Dr Shalal Sadullah, James Paget University Hospital NHS Foundation Trust, and Dr Martin Lewis, The Queen Elizabeth Hospital, King's Lynn.	
Indication for Shared Care	
If an individual requires more than a few days anticoagulation treatment, s/he is generally switched to oral therapy with warfarin or another oral anticoagulant (OAC) (edoxaban, dabigatran, rivaroxaban or apixaban). However there are certain situations where the prolonged use of heparin may be indicated: • medium to long-term thromboprophylaxis for patients in whom oral anticoagulation is contraindicated (e.g. pregnancy). • treatment of venous thromboembolism for patients in whom oral anticoagulation is contraindicated / ineffective (e.g. in pregnancy, interacting drugs, certain patients with cancer, poor compliance.) In these circumstances therapy with LMWH, which does not cross the placenta and is not interfered with by alcohol or other medication, can be given subcutaneously.	
Criteria for patient selection	
Patients requiring therapeutic or prophylactic anticoagulation with LMWH who: **1.** are pregnant (risk of teratogenicity with warfarin; other OACs not licensed) **2.** have poor compliance/life style e.g. alcoholism and drug addiction **3.** have high risk of bleeding e.g. existing thrombocytopenia / certain patients with cancer e.g. receiving myelosuppressive treatment **4.** have thrombosis which is not controlled by an oral anticoagulant – e.g. certain patients with cancer	

Background to treatment

LMWHs have a longer half-life (10-12 hours) than unfractionated heparin (UFH) and can therefore be given by subcutaneous injection on a twice daily or daily basis, and do not need routine anticoagulant monitoring.

LMWHs are at least as effective as UFH in the treatment and prophylaxis of venous thromboembolism (VTE), with a lower or equivalent haemorrhagic risk. They have a lower incidence of heparin-induced thrombocytopenia (HIT) (see below **Side effects**) and less risk of osteoporosis.

LMWHs have replaced UFH for most indications.

Heparin does not cross the placenta or enter breast milk.

Pharmacology

Heparin potentiates the action of anti-thrombin accelerating inactivation thrombin and has direct inactivation of other activated coagulation factors, especially Xa.

Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-IIa activity, and platelet interactions).

Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required.

Licensed uses – please refer to manufacturer's SPCs for full information via http://www.medicines.org.uk/emc/search

- Prophylaxis of VTE (venous thromboembolism) - medical (and surgical)
- Treatment of VTE

(also treatment of unstable angina and non-Q-wave MI / acute ST elevation MI / thrombus prophylaxis in haemodialysis)

Form and strength of preparation

See BNF – LMWHs are available in preloaded syringes, or as vials or ampoules.

N.B The ampoules or vials should NOT be used during pregnancy as they contain preservative.

Side effects - please refer to manufacturer's SPCs for full information via http://www.medicines.org.uk/emc/search

- Haemorrhage:
  Common: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage)
  Uncommon: Intracranial haemorrhage; retroperitoneal haemorrhage
- Local skin reactions/injection-site reactions – generally itchy, erythematous lesions
- **Heparin-Induced Thrombocytopenia (HIT):**
  an immune mediated process where antibodies bind to platelets in the presence of heparin and cause aggregation (thrombosis) and thrombocytopenia – *Uncommon in prophylaxis in medical patients; Common in treatment of patients with DVT, with or without PE*
  Clinical signs of HIT:
  new thrombosis with bleeding; skin necrosis; acute systemic reaction post- heparin bolus. Usually occurs days 5-10 (unless heparin exposure in last 30d) platelets count generally > 20 x 10^9/L no other cause for thrombocytopenia.
- Thrombocytosis (platelet count increased > 400g/l) – *Very common in treatment of patients with DVT, with or without PE*
- Hepatic enzymes increase (transaminases levels > 3 times the upper reference limit) – *Very common*
- Hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis (*rare*))
- Hyperkalaemia secondary to hypoaldosteronism - *rare* (see also **Contraindications & Precautions**)
- Alopecia on prolonged use
- Osteoporosis following long-term therapy (> 3 months)
- Priapism (*rare)*

Healthcare professionals are asked to report any suspected adverse reactions via **Yellow Card Scheme** at: www.mhra.gov.uk/yellowcard

Drug interactions

Anti-platelet drugs – risk of bleeding increased

Nitrates – increase excretion of LMWH – reduced anticoagulant effect

NSAIDs – possible increased risk of bleeding

ACE inhibitors and Angiotensin-II Receptor Antagonists – increased risk of hyperkalaemia.

Contraindications and precautions

Contraindications:

Hypersensitivity/allergy to heparin including HIT.

Each patient must be assessed on an individual basis for risks (bleeding) and benefits (anti-thrombotic effect) of LMWH.

The risks of clinically significant bleeding with LMWH (as with all anticoagulants) are increased if the person has:

an inherited bleeding disorder; thrombocytopenia; recent cerebral haemorrhage; severe liver disease; renal failure; after major trauma or recent surgery - especially to eye (excluding cataract) or nervous system; severe hypertension; active or recent gastric or duodenal ulcer; acute bacterial endocarditis.

Precautions:

Thrombocytopenia: if significant thrombocytopenia consideration should be given to dose reduction in accordance with SPC.

Renal Failure:

LMWH is renally excreted and caution must be taken in patients with severe renal failure.

Consideration should be given to dose reduction and factor Xa monitoring for patients with Creatinine Clearance <30mL/min **(Refn:** Manufacturers' SPCs for *Fragmin*®, *Clexane*® and *Innohep*® - access via **http://www.medicines.org.uk/emc/)**, or at the renal threshold advised by local specialists as being **eGFR <20mL/min/1.73m^2**, depending on extremes of body size.

(See also **Indication for referral back to specialist**)

Hyperkalaemia:

Inhibition of aldosterone secretion by unfractionated or low molecular weight heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy.

Plasma-potassium concentration should be measured in patients at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment will be for longer than 7 days.

Initiation of therapy – *by whom*?

Treatment dose: by hospital

Prophylactic dose: GP in discussion with hospital or hospital consultant

Initial dose and administration

Please see **Appendix 1** for a table of doses currently listed in the BNF, for the indications which relate to those covered under the Shared Care document.

Maintenance dose and administration

As per **Appendix 1**.

Duration of therapy

Treatment:

Generally for 6 weeks to 6 months but may be longer if symptoms or precipitating cause persist. Duration will be indicated on individual patient plan.

Prophylaxis:

Duration will be indicated on individual patient plan.

Other information about administration

Route: Subcutaneous injection

Frequency of administration: Generally once daily or twice daily depending on the LMWH being used. In severe thrombocytopenia, it may be given twice daily.

Initial monitoring

Anticoagulation:

LMWH does not prolong the APTT (unless in overdosage) and can only be monitored by measuring the anti-Xa activity. This is not a routinely available assay. However **no routine anticoagulant monitoring is required**. Very occasionally monitoring may be indicated - this will be clearly outlined in the individualised patient plan and if necessary will be arranged by the hospital.

Platelet count:

There is a risk of HIT associated with LMWH (a drop in platelets associated with thrombosis; see earlier under **Side effects**).

HIT should be suspected if bleeding or bruising develops or there is a sudden worsening of thrombotic problems associated with bleeding. A reasonable level of **suspicion** is therefore important.

The commonest time for HIT to occur is between 5 and 21 days following the beginning of therapy.

Patients should be warned to look for evidence of recurrence of thrombosis or bleeding and to report immediately. If there is concern regarding HIT the FBC should be checked.

It is recommended that platelet counts be measured before the initiation of therapy with LMWH and then regularly thereafter during the treatment (Refn Clexane SPC). If there is a 30 to ≥ 50% drop in platelet count or worsening thrombosis with bleeding, stop LMWH treatment and seek advice from the On-Call Haematologist.

Osteoporosis:

Bone density measurement is not generally indicated for relatively short-term treatment (up to 3 months). This would be arranged by the hospital if appropriate.

For patients on treatment doses the NNUH recommend that:

the patient is reweighed every 3 months to check if the dose is still appropriate (except in pregnant women where the booking date is used),

and that the need to remain on LMWH is confirmed with the initiator (generally hospital physician)

and if there is concern regarding renal function, that this is checked.

Specialist monitoring

All patients have baseline platelet count and renal function and potassium.

(Refn: BCSH guidance Diagnosis and Management of Heparin Induced Thrombocytopenia: Second Edition- British Journal of Haematology, 2012, 159, 528–540)

GP monitoring

No routine anticoagulant or FBC monitoring required.

It is recommended that platelet counts be measured regularly during treatment with LMWH (Refn Clexane SPC). If there is a 30 to ≥ 50% drop in platelet count or worsening thrombosis with bleeding, stop treatment and seek advice from the On-Call Haematologist.

Renal function and potassium should be checked 3-monthly in patients deemed at risk of developing renal impairment or hyperkalaemia. If eGFR drops to <20 mL/min/1.73m^2 contact initiating specialist.

Consultant / Specialist prescribing responsibilities

Initiation of LMWH for patients on treatment regimen and produce individual management plan for duration and dosage.

To provide advice regarding the indications for prophylactic LMWH.

GP prescribing responsibilities

Following advice from hospital consultant:

- to start other indications for prophylactic prescriptions (unless there are contraindications)
- to continue the prescription for treatment and prophylaxis as and when necessary.

Indication for referral back to specialist

Patient reports problems such as bleeding, suspicion of thrombosis, reactions

Significant bleeding: *Stop LMWH* – seek advice from anticoagulant practitioners or On Call Haematologist

Life threatening haemorrhage: *Stop LMWH*. Admit via hospital Medical Assessment Unit

Suspected HIT: 30 to ≥ 50% drop in platelet count (usually platelets are > 20 x 10^9/L in HIT) or worsening thrombosis with bleeding – *Stop LMWH* and seek advice from On Call Haematologist

Localised skin reactions: Consider change to another brand (N.B. note different dosages)

Development of renal failure (defined as <20mL/min/1.73/m^2): assessment of risks and benefits of the patient staying on therapeutic anticoagulation is required; including consideration of the indication for anticoagulation, the cause of renal impairment (including the potential for reversibility), and the clinical state of the patient.

Haematology Department Contacts – Norfolk & Norwich University Hospital (01603 286286)

Anticoagulant practitioners: Tel: 01603 286286 and request Bleep 799

or **On Call Haematologist** via the NNUH switchboard

Haematology Department Contacts – The James Paget University Hospital (Tel 01493 452452)

On Call Consultant Haematologist: Through the JPUH switch board

Anticoagulant Nurses: Tel/Fax: 01493 453213 Bleep 1473 via switchboard

Haematology Department Contacts – The Queen Elizabeth Hospital (Tel 01553 613613)

On call Haematologist: Through the QEH switch board

Clinical Nurse Specialist: Tel: 01553 613355

Patient information

The manufacturer's Patient Information Leaflet for the LMWH product prescribed will be used as the basis for counselling patients. This is available as a package insert or otherwise via www.medicines.org.uk. Training for subcutaneous administration will be given to such patients and can be arranged at the hospital for patients on prophylactic heparin (if necessary).

Additional information

British Journal of Haematology, 2012, 159, 528–540

Appendix 1: Dosage Information for LMWHs

LMWH	Prophylaxis of DVT in adults with medical conditions who otherwise cannot have oral anticoagulants: Given by s/c injection as a once daily dose	Treatment of DVT and PE in adults with medical conditions who otherwise cannot have oral anticoagulants: Given by s/c injection as a once daily dose by body-weight (kg)	Treatment of VTE in pregnancy: Given by s/c injection as a twice daily dose by early pregnancy body-weight (kg)	Extended treatment and prophylaxis of VTE in adults with solid tumours: Given by s/c injection as a once daily dose by body-weight
Dalteparin (*Fragmin*®)	5000 units once daily *	< 46kg: 7500 units 46-56kg: 10 000 units 57-68kg: 12 500 units 69-82kg: 15 000 units 83kg plus: 18 000 units	< 50kg: 5000 units twice daily 50-69kg: 6000 units twice daily 70-89kg: 8000 units twice daily 90kg plus: 10 000 units twice daily	**For first 30 days:** 40-45kg: 7500 units once daily 46-56kg: 10 000 units once daily 57-68kg: 12 500 units once daily 69-82kg: 15 000 units once daily 83kg plus: 18 000 units once daily **For a further 5 months:** 40-56kg: 7500 units once daily 57-68kg: 10 000 units daily 69-82kg: 12 500 units daily 83-98kg: 15 000 units daily 99kg plus: 18 000 units daily
Enoxaparin (*Clexane*®) ***1mg = 100 units***	40mg once daily for a minimum of 6 days and until the return to full ambulation, for a maximum of 14 days	1.5mg/kg once daily	< 50kg: 40mg twice daily 50-69kg: 60mg twice daily 70-89kg: 80mg twice daily 90kg plus: 100mg twice daily	No dosage info available in BNF
Tinzaparin (*Innohep*®)	No dosage in BNF	175 units/kg once daily	175 units/kg once daily	175 units/kg once daily; max 6 months

Refn BNF: Accessed May 2017 - https://www.medicinescomplete.com/mc/bnf/current/PHP1453-low-molecular-weight-heparins.htm

*** NNUH recommendations regarding prophylactic use of dalteparin (Fragmin®):**

For low weight patients (< 50kg) consider a dosage reduction to 2500iu dailiy.

For patients >100kg consider 5000Iu BD

Version Control and revision history

Version	Date	Author/Editor	Status	Comment
1.	January 2004	Dr Jennie Wimperis, NNUH in consultation with Dr Jane Keidan (QEH) and Dr Shalal Sadullah (JPUH)	Superseded	Therapeutics Advisory Group (TAG) approved
2.	November 2007 to March 2008	Dr Jennie Wimperis, NNUH in consultation with Dr Natasha Curtin (QEH) and Dr Shalal Sadullah (JPUH).	Superseded	Patient criteria and prescribing responsibility reviewed and clarified. Hospital authors and contacts updated. V2 published March 2008.
3.0	July 2014	To be confirmed / Editor – Fiona Marshall, TAG Lead Pharmacist, NEL CSU Anglia.	Draft	Interim version whilst negotiations over provision of treatment and prevention of thromboembolism in line with national guidance are on-going. Updated regarding general principles of shared care, formatting, ownership, authors, dosages and indications. Checked against current information regarding interactions, ADRs, side-effects, contraindications and precautions. Info regarding risk of hyperkalaemia and monitoring requirements inserted.
3.1	August 2014	Dr Jennie Wimperis, NNUH / Editor – Fiona Marshall, TAG Lead Pharmacist, NEL CSU Anglia.	Draft	Support for suggested changes plus further recommendations for changes received from Dr Jennie Wimperis (NNUH); relating to dosing in renal failure, overweight and low weight patients, monitoring requirements and indications for referral back to the specialist, dosage near delivery in pregnancy, References to use of NOACs added. Reference and link to BCSH guidance added to additional information.
3.2	September 2014	Dr Jennie Wimperis, NNUH / Editor – Fiona Marshall, TAG Lead Pharmacist, NEL CSU Anglia.	Current	Changes noted and supported by the TAG September 2014. Details confirmed with local specialists after the TAG meeting.
4.0	May – Sept 17	TBC, NNUH, Dr Shalal Sadullah, JPUH, and Dr Martin Lewis, QEH / Editor – Fiona Marshall, TAG Lead Pharmacist, NEL CSU Anglia	Draft	Updated in line with current BNF and manufacturers' SPCs. Suggested amendments in Red font. For consideration by local specialists. No comments received May to August 2017. Supported for continued use by the TAG September 2017 in the interim.
5.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures