Prescribing of Low Molecular Weight Heparin in Wales

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This document has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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This document should be cited as:
CONTENTS

1.0 INTRODUCTION .................................................................................................... 2
2.0 RECOMMENDATIONS .......................................................................................... 3
3.0 PRACTICAL CONSIDERATIONS .......................................................................... 3
  3.1 Choice of LMWH ................................................................................................ 3
  3.2 Shared care implications .................................................................................... 3
  3.3 Hospital prescribing implications ......................................................................... 4
  3.4 Monitoring........................................................................................................... 4
  3.5 Advice to patients ............................................................................................... 4
  3.6 Appropriate use of NHS resources ...................................................................... 4
  3.7 GP registers ....................................................................................................... 4
  3.8 Prescribing for patients treated out of area or by private providers sector ....... 5
  3.9 LMWH for licensed indications ............................................................................ 5
    3.9.1 Perioperative anticoagulation .................................................................... 5
    3.9.2 Postoperative thromboprophylaxis ............................................................. 5
    3.9.3 Treatment of suspected DVT whilst awaiting investigation ...................... 5
  3.10 Off-label use of LMWH ..................................................................................... 5
    3.10.1 LMWH for sub-therapeutic INRs ............................................................... 6
    3.10.2 Cancer patients requiring anticoagulation for atrial fibrillation ............... 6
    3.10.3 Patients considering pregnancy ................................................................. 7
    3.10.4 Prophylactic LMWH for weight related risk during pregnancy ............... 7
    3.10.5 Postpartum ................................................................................................ 7
REFERENCES ............................................................................................................. 8
APPENDIX 1: LICENSED INDICATIONS AND AWMSG RECOMMENDATIONS ...... 9
APPENDIX 2. VELINDRE CANCER CENTRE UPTAKE DATA FOR SHARED CARE 11
1.0 INTRODUCTION

In the prevention and treatment of venous thromboembolism (VTE), low molecular weight heparins (LMWHs) (dalteparin, enoxaparin, tinzaparin) are generally preferred over unfractionated heparin. They are as effective as heparin and have a lower risk of heparin-induced thrombocytopenia. There is a reduced requirement for monitoring, the duration of action is longer than that of unfractionated heparin and once-daily subcutaneous administration is possible for some indications, making them convenient to use. LMWHs are also used in the treatment of myocardial infarction, unstable coronary artery disease and for the prevention of clotting in extracorporeal circuits (see Appendix 1 for full list of licensed indications), and a number of off-label indications are commonly prescribed.

In recent years there has been an increase in the primary care prescribing of LMWH, where previously treatment was through specialists and the acute sector. In the five years to 2015–2016, primary care prescribing has increased by 11.48%.

There are divergent professional views on the most appropriate place for the prescribing of LMWH. A GP may rarely encounter such medicines commonly used by a specialist. Concerns have been expressed at the lack of information or guidance to support these prescribers, and the need to refer to individual product information has been emphasised. Lack of familiarity with medication is an important cause of medication errors and it is therefore essential that care is only shared where it is in the best interests of the patient.

Appendix 2 provides an example of good practice, along with uptake data, for shared care prescribing of LMWHs in Velindre Cancer Centre.
2.0 RECOMMENDATIONS

**Recommendation 1**
LMWH treatment for four weeks or less should be prescribed and monitored by the initiating prescriber (any indication), and if extended, the course of treatment should continue to be prescribed and monitored by the initiating prescriber.

**Recommendation 2**
Where there is a need to monitor LMWH treatment by measuring the anti-Xa level, patients should be prescribed and followed up regularly by specialist services.

**Recommendation 3**
Treatment doses of LMWH prescribed for VTE in cancer patients (i.e. patients undergoing cancer therapy or those who have metastatic disease) are suitable for shared care for up to six months of treatment. Shared care should be agreed in writing with an invitation to participate by consultant and response from the GP. There should be a point of review at 6 months to confirm whether LMWH is still necessary.

**Recommendation 4**
Treatment doses of LMWH for VTE in pregnancy should be ‘hospital only’ prescribing.

**Recommendation 5**
Prophylactic doses of LMWH in pregnancy for medical conditions should normally be prescribed by secondary care*. Mechanisms need to be agreed locally to support adequate supply between appointments (30–42 days).

*This recommendation excludes the indication of obesity as further discussions are needed regarding the prescribing of prophylactic doses for obese patients.

These recommendations are intended to provide more guidance and support to prescribers. They will not affect those regions which, on agreement with relevant directorates and Medicines and Therapeutics Committees, prefer to prescribe all LMWH from secondary/tertiary care.

Where they relate to hospital-only prescribing, these recommendations will not restrict the ability of a GP to prescribe when there is mutual agreement with a specialist that this is more appropriate for an individual patient.

3.0 PRACTICAL CONSIDERATIONS

3.1 Choice of LMWH
AWMSG is not providing guidance on the choice of LMWH; however, a table detailing available LMWH products and their licensed indications, correct at the time of publication [September 2016], as well as AWMSG recommendations made in relation to specific LMWHs, is included in Appendix 1. For the latest information please consult the eMC and AWMSG websites.

3.2 Shared care implications
It should be noted that where shared care is recommended, the arrangement should be confirmed in writing between the specialist and the GP. If shared care is agreed, the GP will undertake prescribing after the first month and ensure that any necessary monitoring (e.g. full blood count [FBC]/electrolytes [U+Es]) is undertaken. A shared care protocol should be developed with details of the necessary monitoring, together with the roles and responsibilities of primary and secondary care teams. A generic shared care template is available on the AWMSG website for health boards to use.

Shared care is not considered appropriate under Recommendation 1, because of potential delays in communication and increased monitoring during this period.
3.3 Hospital prescribing implications
It is recognised that patients should not attend consultant out-patient appointments simply to collect a prescription. Systems have been developed by different localities and directorates to avoid this.

3.4 Monitoring
Requirements for monitoring prior to initiation vary between LMWH Summaries of Product Characteristics (SPCs). Based on feedback from the service, it would seem prudent that all patients have an FBC and U+E profile prior to initiation to facilitate appropriate monitoring and any subsequent necessary dose adjustments. Monitoring requirements should be specified in a shared care protocol. As stated in Recommendation 1, ‘LMWH treatment for four weeks or less should be prescribed and monitored by the initiating prescriber (any indication)’.

3.5 Advice to patients
It is essential that patients understand the rationale for anticoagulation therapy, how to safely self-administer LMWH and dispose of the sharps. Healthcare professionals should ensure that the patient has a sharps bin, and knows how it will be collected and who to contact if there is a problem.

Anecdotal reports suggest that advice given to patients prescribed LMWH can be inadequate. Some LMWH patient information leaflets provide pictorial advice on administration. Patients must be counselled regarding the risks and benefits of LMWH therapy before prescribing. Patients require advice and education regarding self-administration of treatment.

The National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG) 76 states that: ‘between a half and third of all medicines prescribed for long-term conditions are not taken as recommended... If the prescription was appropriate then this may represent a loss not just for patients but also for the healthcare system and society... Non-adherence is a large problem but it should not be seen as the patient’s problem. Rather, it represents a limitation in the delivery of healthcare, often due to a failure to fully agree the prescription in the first place or to identify and provide the support that patients need later on’.

It is therefore good practice to encourage patients to self-administer one dose of their LMWH under supervision at the start of treatment, to confirm that they are capable and confident in the use of their medication.

3.6 Appropriate use of NHS resources
Prescribers should ensure that the prescription duration is appropriate for the indication, according to local or national guidelines.

When high volumes of LMWH are prescribed there is a risk of waste. However, prescribing smaller volumes could affect adherence.

It is not appropriate for patients to attend outpatient departments simply to obtain sharps bins. These are prescribable and local arrangements exist for their collection and disposal. Patient information leaflets on the local schemes should be available.

3.7 GP registers
Prescribers should consider establishing a register and recall system for patients taking LMWH.
3.8 Prescribing for patients treated out of area or by private providers sector
Patients treated within Wales should be treated according to NICE CG92\(^4\), whether the operation or treatment was undertaken by NHS Wales or a private provider, e.g. patients undergoing orthopaedic surgery would expect to receive thromboprophylaxis from the specialist rather than a GP, as outlined in section 3.9.2.

Patients should be provided with consistent and safe advice within their packages of care.

3.9 LMWH for licensed indications

3.9.1 Perioperative anticoagulation
Perioperative anticoagulant advice should be provided by the hospital. If LMWH is recommended, responsibility for advising the patient, informing the GP and prescribing should normally be undertaken by the hospital. This aims to ensure that patients are provided with consistent timely advice and treatment by professionals familiar with perioperative anticoagulation.

Patients will be attending a preoperative assessment clinic and those prescribed an oral anticoagulant are usually advised to switch to LMWH or aspirin during the perioperative period. The duration of alternative therapy is usually less than a week but advice will be dependent on the complexity of the surgery and underlying thromboembolic risk.

3.9.2 Postoperative thromboprophylaxis
NICE CG92 on Venous thromboembolism: reducing the risk for patients in hospital makes recommendations on assessing and reducing the risk of VTE in patients in hospital and refers healthcare professionals to the appropriate SPC for advice in relation to prescribing an LMWH in postoperative thromboprophylaxis\(^4\).

The majority of this postoperative LMWH prescribing is likely to come under AWMSG Recommendation 1: ‘LMWH treatment for four weeks or less should be prescribed and monitored by the initiating prescriber (any indication), and if extended, the course of treatment should continue to be prescribed and monitored by the initiating prescriber’. Healthcare professionals should refer to the individual SPCs for information on the duration of treatment.

3.9.3 Treatment of suspected DVT whilst awaiting investigation
This is a licensed indication for LMWH. Currently, the majority of LMWH prescribing for this indication is taking place in secondary care. However, work is underway to develop new pathways as there is increasing interest in and requests for GP prescribing for this indication.

3.10 Off-label use of LMWH
It is recognised that off-label prescribing of LMWH is common across health boards in Wales; such prescribing should be ratified through the appropriate prescribing committees within those health boards to provide local prescribers with clear information.

Use of LMWHs outside of their licensed indication as ‘off-label’ medicines is not recommended by the market authorisation holders. General Medical Council (GMC) advice for off-label prescribing in these circumstances should be followed.

Various scenarios of off-label LMWH prescribing occur. Prescribing responsibility for these unlicensed and exceptional uses will need to be taken on an individual patient basis.
3.10.1 LMWH for sub-therapeutic INRs
Patients on warfarin who are at high risk of thromboembolism should be prescribed LMWH if the international normalised ratio (INR) becomes sub-therapeutic. LMWH prescribing in these circumstances should be undertaken by the department responsible for dosing warfarin.

Increasing numbers of patients in primary care are taking warfarin. It has been questioned whether LMWH should be prescribed when the INR is sub-therapeutic. Consensus suggests that this should occur when the INR is below 2 unless otherwise specified by the specialist. Prescribing LMWH for sub-therapeutic INRs is only necessary in a small cohort of high risk patients, e.g. patients with recurrent VTE and those with mechanical heart valves, if recommended by the cardiac surgeon.

A mechanism for providing LMWH to patients at high risk of thromboembolism should be included within practice policy and high risk patients should be identified within the register of patients receiving anticoagulation.

Use of LMWH for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation is off label and GMC advice for off-label prescribing in these circumstances should be followed.

3.10.2 Cancer patients requiring anticoagulation for atrial fibrillation
If patients on anticoagulation therapy subsequently develop cancer, their risks for thromboembolism and bleeding will change. There is a lack of clarity regarding the safest choice of anticoagulant in these patients. If uncertainty persists after considering the balance of risks and benefits, then the advice of a cardiologist or stroke physician should be sought.

Given the heterogeneous nature of patients with cancer, their risks and benefits for continued anticoagulation should be assessed individually. To help predict the risk of stroke, several scoring systems have been developed such as CHA2DS2-VASc (see Table 1). These aid decision-making regarding the most appropriate thromboprophylaxis and should be considered together with the bleeding risk and thromboembolic risk arising from the cancer. AWMSG and the Welsh Medicines Resource Centre (WeMeReC) have both produced guidance on atrial fibrillation, providing full discussion of thromboembolic and bleeding risk assessments\(^5\,^6\).

### Table 1. CHA2DS2-VASc scoring system (stroke risk stratification scheme)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C Heart failure/left ventricular dysfunction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A(_2) Age ≥ 75</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>S(_2) Stroke/transient ischaemic attack/thromboembolism</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>V Vascular disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A Age 65–74</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sc Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.10.3 Patients considering pregnancy
It is essential that patients with a high risk of thromboembolism receive preconception counselling at an early stage, via referral to an obstetrician or obstetric/haematology team for expert advice.

LMWH does not need to be initiated prophylactically in these patients before a pregnancy is confirmed.

The Royal College of Obstetrics and Gynaecology (RCOG) states: ‘Antenatal thromboprophylaxis for those with previous VTE should begin as early in pregnancy as practical... Individuals with recurrent VTE are at increased risk of further recurrence and many will be on long-term oral anticoagulant therapy. Although data are lacking, it would be expected that they would have a high risk of recurrence in pregnancy... Advice regarding doses of LMWH in pregnancy should be sought from a clinician with expertise in haemostasis and pregnancy... Women on long-term warfarin or other oral anticoagulants should be counselled about the risks of these agents to the fetus (see section 8.6) and advised to stop their oral anticoagulant therapy and change to LMWH as soon as pregnancy is confirmed, ideally within two weeks of the missed period and before the sixth week of pregnancy. Women not on warfarin or other oral anticoagulants should be advised to start LMWH as soon as they have a positive pregnancy test.’

Healthcare professionals should refer to SPCs for advice in relation to prescribing LMWHs in pregnancy.

3.10.4 Prophylactic LMWH for weight related risk during pregnancy
AWMSG Recommendation 5 states that ‘prophylactic doses of LMWH in pregnancy for medical conditions should normally be prescribed by secondary care’.

No recommendations are made for prescribing for pregnant patients where the indication is weight related risk. Both NICE⁴ and the RCOG⁷ have published updated guidance to reduce the risk of thrombosis and embolism. Both contain recommendations which would have significant implications for patients and NHS Wales. AWMSG will be unable to make recommendations for prescribing LMWH in pregnant women with a high body mass index (BMI) until ‘standard practice’ is agreed by national bodies.

3.10.5 Postpartum
Most patients recommended postnatal LMWH will only require seven days treatment. Six weeks supply is appropriate in high risk groups only.

LMWH is appropriate for postpartum thromboprophylaxis although if women are receiving long-term anticoagulation with warfarin this can be started when the risk of haemorrhage is low, usually 5–7 days after delivery⁷.

Healthcare professionals should refer to SPCs for advice in relation to prescribing LMWHs postpartum.
REFERENCES


USEFUL RESOURCES

In February 2011, WeMeReC produced a bulletin and a slide set on LMWH.
### APPENDIX 1: LICENSED INDICATIONS AND AWMSG RECOMMENDATIONS

#### Dalteparin

| Fragmin® 10,000 IU/0.4ml solution for injection | Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both. Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence. |
| Fragmin® 12,500 IU/0.5ml solution for injection | Prevention of clotting in the extracorporeal circulation during haemodialysis or haemofiltration, in patients with chronic renal insufficiency or acute renal failure. |
| Fragmin® 15,000 IU/0.6ml solution for injection | Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both. Unstable angina and non-Q wave myocardial infarction (unstable coronary artery disease-UCAD), administered concurrently with aspirin. Extended Use Fragmin may be used beyond 8 days in patients awaiting angiography/revascularisation procedures (see Section 5.1) |
| Fragmin® 18,000 IU/0.72ml solution for injection | Prevention of clotting in the extracorporeal circulation during haemodialysis or haemofiltration, in patients with chronic renal insufficiency or acute renal failure. |

| Fragmin 10,000 IU/1 ml | Prevention of clotting in the extracorporeal circulation during haemodialysis or haemofiltration, in patients with chronic renal insufficiency or acute renal failure. |
| Fragmin 10,000 IU/4ml Multidose Vial | Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both. |
| Fragmin® 2500 IU | Peri- and post-operative surgical thromboprophylaxis. |

| Fragmin® 5000 IU | Peri- and post-operative surgical thromboprophylaxis. The prophylaxis of proximal deep venous thrombosis in patients bedridden due to a medical condition, including, but not limited to; congestive cardiac failure (NYHA class III or IV), acute respiratory failure or acute infection, who also have a predisposing risk factor for venous thromboembolism such as age over 75 years, obesity, cancer or previous history of VTE. Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence. |
| Fragmin® 7,500 IU/0.3 ml solution for injection | Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both. Unstable angina and non-Q wave myocardial infarction (unstable coronary artery disease-UCAD), administered concurrently with aspirin. Extended Use Fragmin may be used beyond 8 days in patients awaiting angiography/revascularisation procedures (see Section 5.1) |
| Fragmin® Graduated Syringe 10,000 IU/ml Solution for Injection | Unstable angina and non-Q wave myocardial infarction (unstable coronary artery disease-UCAD), administered concurrently with aspirin. Extended Use Fragmin may be used beyond 8 days in patients awaiting angiography/revascularisation procedures (see Section 5.1) |

#### Enoxaparin

| Clexane® Forte Syringes | The prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopaedic or general surgery. The prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness. The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both. The treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin. Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI) in conjunction with thrombolytic drugs (fibrin or non-fibrin specific). The prevention of thrombus formation in the extracorporeal circulation during haemodialysis. |
| Clexane® Multidose Vial | |
| Clexane® pre-filled syringes | |

| AWMSG advice | Enoxaparin (Clexane®) is recommended as an option for use within NHS Wales for the treatment of acute ST-segment elevation myocardial infarction (STEMI). AWMSG is of the opinion that enoxaparin (Clexane®) is not suitable for shared care within NHS Wales. |
### Tinzaparin

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>innohep 10,000 IU/ml</strong></td>
<td>For the prevention of thromboembolic events, including deep vein thrombosis, in adults undergoing general and orthopaedic surgery. For the prevention of clotting in the extracorporeal circuit during haemodialysis in adults with chronic renal insufficiency.</td>
</tr>
<tr>
<td><strong>innohep 20,000 IU/ml</strong></td>
<td>Treatment of deep vein thrombosis and of pulmonary embolus in adults.</td>
</tr>
</tbody>
</table>

| AWMSG advice          | Tinzaparin sodium (innohep® Syringe) is recommended as an option for use within NHS Wales for the extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in adult patients with solid tumours. |
APPENDIX 2. VELINDRE CANCER CENTRE UPTAKE DATA FOR SHARED CARE

An example of good practice, along with uptake data, for shared care prescribing of LMWH has been provided by Velindre Cancer Centre.

Background
Malignant disease is one of the main risk factors for the development of thrombosis. The link is so close that the National Institute for Health and Care Excellence (NICE) Clinical Guideline 144 (2015) on Venous Thromboembolic Disease recommends that patients diagnosed with unprovoked clots be sent for investigations to rule out malignant disease (recommendation 1.5).

Velindre Cancer Centre (VCC) serves a South East (SE) Wales wide population, with 99% of patients coming from either Cardiff and Vale, Cwm Taf, Aneurin Bevan or Abertawe Bro Morgannwg University Health Board.

As a result of the CLOT trial (2003), low molecular weight heparins (LMWH) have been the treatment of choice for the treatment of cancer-associated thrombosis (CAT); this has also been endorsed by NICE and all the major oncological committees (American Society of Clinical Oncology [ASCO] and the European Society of Medical Oncology [ESMO]).

The main problem
Historically, patients would obtain all of their LMWH supply from VCC. This is less of an issue for patients returning to VCC for treatment. However, after a patient’s course of treatment had completed, they would need to return to VCC for no reason other than to pick up more LMWH, and as VCC treats patients from all SE Wales, this could be a long journey for many patients.

These patients (who had completed their course of treatment) would phone/arrive at VCC without any appointment as they had finished their treatment, and would often get directed to pharmacy to obtain more LMWH. There would then be a lot of phoning around, trying to contact consultant teams and trying to get prescriptions written. This often took hours and was very distressing for the patient.

CAT service
In January/February 2014, a CAT service was set up in VCC; this was focused around a dedicated CAT clinic run by Dr Simon Noble. A sister clinic was also set up in the Royal Gwent Hospital. The CAT clinic not only provided patients with easier access to ongoing treatment but also provided them with expert information and support.

The CAT clinic solved one of the main problems for patients who had completed their cancer treatment who were still on LMWH therapy. Patients would be referred to the CAT clinic for appropriate review and to obtain further supply of LMWH.

However, this did not prevent patients having to make a long journey. In response to this problem the CAT service developed a shared care protocol in May 2014.

Shared care protocols
The adaptation of shared care protocols for the treatment of CAT significantly improved the patient pathway for this patient group.

Today, patients not only have access to a dedicated specialist CAT service but also local access to LMWH.
In the last two years, the CAT service has won an NHS Wales award for Promoting Clinical Research and Application to Practice (2015) and a Quality In Care (QIC) programme award for Best Cross-Organisational Partnership (2014).

However, local access to LMWH is still only accessible for patients in Cardiff and Vale University and Aneurin Bevan University Health Boards.

**Uptake**

From May 2014–June 2016, 100 shared care protocol requests have been sent from VCC to primary care (Cardiff and Vale and Aneurin Bevan).

94 of the 100 requests have been accepted by GPs. There was one non-responder.

Of the five who did not accept, the reasons were as follows:

- Lack of experience with prescribing LMWH
- Heavy workload
- Hospital-only prescription
- Patient has a Cardiff and Vale postcode, GP has a Cwm Taf postcode
- Practice does not partake in shared care

**Future work**

Continue working with Cwm Taf and Abertawe Bro Morgannwg University Health Boards to adopt shared care; this will ensure that all cancer patients across SE Wales with cancer-associated thrombosis have the same level of access regardless of where they live.