

PROTOCOL: CV 56 DALTEPARIN▼ for the treatment of Venous Thromboembolisms (VTE) in patients with solid tumours

This document should be read in conjunction with the current Summary of Product Characteristics (SPC)
<http://www.medicines.org.uk/>

General Guidance	<p>This protocol outlines the shared care arrangements for patients with solid tumours receiving dalteparin (Fragmin▼) for the extended treatment of symptomatic venous thromboembolism (VTE) and prevention of recurrence.</p> <p>This is endorsed for use across Cardiff and Vale UHB on the understanding that the shared care arrangement covers up to a maximum of 6 months treatment, which is currently the licensed duration of treatment/ prophylaxis for dalteparin in patients with solid tumours.</p>
1. Licensed Indications	<p>Patients with solid tumours: Extended treatment (up to six months) of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.</p>
2. Therapeutic use & background	<p>VTE is a major complication of cancer (occurring in 4% to 20% of patients) and is one of the leading causes of death in patients with cancer. The risk appears to be greater for those patients who are hospitalised and/or receiving active treatment; certain newer treatment regimens that include thalidomide, lenalidomide, or bevacizumab have reported very high rates of VTE.</p> <p>Low molecular weight heparin (LMWH) represents the preferred agent for both the initial and continuing treatment of cancer patients with established VTE.¹ Dalteparin is currently the only licensed LMWH for these indications and then only for a 6 month period. For certain patients i.e. those with progressive disease this duration needs to be life long however, there is no trial evidence to support this.</p> <p>Dalteparin cannot be used interchangeably with other LMWHs.</p>
3. Contraindications	<p>Patients with the following conditions are excluded from this protocol:</p> <ul style="list-style-type: none">• Known or suspected hypersensitivity to dalteparin or other LMWHs and/or heparins.• History of immunologically mediated Heparin Induced Thrombocytopenia (HIT).• Patients requiring anti Xa-monitoring• Renal impairment (calculated creatinine clearance < 30ml/min).• Significant hepatic impairment.• Active gastric/duodenal ulceration or oesophageal varices.• Haemophilia and other inherited/major bleeding disorders or any unusual

	<p>susceptibility to bleeding or haemorrhagic pericardial/ pleural effusion.</p> <ul style="list-style-type: none"> • Thrombocytopenia with platelets < 50. • Recent (within 3 months) cerebral haemorrhage (stroke due to systemic emboli excepted). • Severe hypertension. • Sub-acute endocarditis. • Children under 16 years. • Low body weight (< 40kg at time of venous thromboembolic event). • Pregnancy. • In patients receiving dalteparin for treatment (rather than prophylaxis), local and/or regional anaesthesia in elective surgical procedures is contra-indicated. • Recent neurosurgery or eye/ear surgery. • Injuries to the central nervous system, eyes and ears. <p><i>NB: In accordance to the manufacturers Summary of Product Characteristics (SPC) as stated above, the use of LMWHs (Dalteparin®) is contra-indicated after injuries to or operations on the eyes or ears. However, expert opinion suggests that provided there is no active bleeding, LMWHs (Dalteparin) may be used in this patient group outside the acute healing phase post eye or ear surgery/injury.² Therefore it is recommended that LMWH may be used 3 months after eye/ear surgery.</i></p>
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<p>4. Typical Dosage Regimen (Adults)</p>	<p>Month 1 Administer Dalteparin at approximately 200 IU/kg total body weight subcutaneously (S/C) once daily for the first 30 days of treatment (see table below).</p> <p>Dalteparin should not be administered by the intramuscular route.</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Body weight</th> <th>Dose (IU)</th> </tr> </thead> <tbody> <tr> <td>< 46kg</td> <td>7,500</td> </tr> <tr> <td>46kg to 56kg</td> <td>10,000</td> </tr> <tr> <td>57kg to 68kg</td> <td>12,500</td> </tr> <tr> <td>69kg to 82kg</td> <td>15,000</td> </tr> <tr> <td>83kg and over</td> <td>18,000</td> </tr> </tbody> </table> <p style="margin-left: 200px;">The total daily dose should not exceed 18,000 IU daily. Maximum dose of 18,000 IU was used in patient weighing up to 132 kg in the CLOT study.</p> <p>Months 2-6 Dalteparin should be administered at a dose of approximately 150 IU/kg S/C once daily using fixed dose syringes (see table below).</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Body weight</th> <th>Dose (IU)</th> </tr> </thead> <tbody> <tr> <td>≤ 56kg</td> <td>7,500</td> </tr> <tr> <td>57kg to 68kg</td> <td>10,000</td> </tr> <tr> <td>69kg to 82kg</td> <td>12,500</td> </tr> <tr> <td>83kg to 98kg</td> <td>15,000</td> </tr> <tr> <td>≥ 99kg</td> <td>18,000</td> </tr> </tbody> </table>	Body weight	Dose (IU)	< 46kg	7,500	46kg to 56kg	10,000	57kg to 68kg	12,500	69kg to 82kg	15,000	83kg and over	18,000	Body weight	Dose (IU)	≤ 56kg	7,500	57kg to 68kg	10,000	69kg to 82kg	12,500	83kg to 98kg	15,000	≥ 99kg	18,000
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	<p>Recommended duration of treatment is 6 months, and continuing treatment beyond this period will be evaluated according to individual risk/benefit ratio, taking into account particularly the progression of cancer. No data is available with Dalteparin beyond 6 months of treatment in the CLOT study.</p> <p>In practice an individual specialist clinician may choose to extend the duration beyond six months, however this shall be in the context of an off licence prescription. In this circumstance the prescribing responsibility will revert back to the specialist in the secondary / tertiary care setting.</p>										
<p>5. Drug Interactions. For a comprehensive list, consult product SPC</p>	<ul style="list-style-type: none"> • Drugs affecting haemostasis (such as aspirin, dipyridamole, NSAIDs, clopidogrel, thrombolytics and anticoagulants) should be discontinued prior to Dalteparin therapy unless their use is essential,. • Dalteparin may increase the risk of hyperkalaemia in patients on potassium-sparing drugs (e.g. ACE inhibitors). 										
<p>6. Adverse drug reactions</p> <p>For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult SPC</p>	<p>Several toxicities are seen with long-term use and may therefore present first to GPs.</p> <p>Adverse reaction can be classified as either very common ($\geq 10\%$), common ($\geq 1\%$ and $< 10\%$); uncommon ($\geq 0.1\%$ and $< 1\%$).</p> <table border="1" data-bbox="411 1182 1495 1608"> <thead> <tr> <th><i>Clinical condition (reported frequency)</i></th> <th><i>Management</i></th> </tr> </thead> <tbody> <tr> <td>Major haemorrhage (<1%)</td> <td>Stop drug and seek urgent attention</td> </tr> <tr> <td>Skin necrosis usually at the site of injection (<1%) (usually on commencing drug)</td> <td>Stop drug and discuss</td> </tr> <tr> <td>Cutaneous or systemic allergic reaction (>1%; <10%)</td> <td>Stop drug and discuss</td> </tr> <tr> <td>Pain, haematoma and mild local irritation at injection site (>1%; <10%)</td> <td>No need to discontinue therapy common, may be self-limiting</td> </tr> </tbody> </table> <p>Other side effects:</p> <ul style="list-style-type: none"> • Long term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with dalteparin, the risk of osteoporosis cannot be excluded • Heparin 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, a raised plasma potassium or taking potassium sparing drugs. <p>Patients should be particularly warned to report <u>any bleeding</u>.</p>	<i>Clinical condition (reported frequency)</i>	<i>Management</i>	Major haemorrhage (<1%)	Stop drug and seek urgent attention	Skin necrosis usually at the site of injection (<1%) (usually on commencing drug)	Stop drug and discuss	Cutaneous or systemic allergic reaction (>1%; <10%)	Stop drug and discuss	Pain, haematoma and mild local irritation at injection site (>1%; <10%)	No need to discontinue therapy common, may be self-limiting
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	All serious adverse events should be reported to MHRA/CHM via the 'Yellow Card' scheme.
7. Baseline investigations	<p>To be undertaken by secondary / tertiary care:</p> <ul style="list-style-type: none"> • FBC • Clotting screen (PT and APTT and fibrinogen) • Creatinine and electrolytes (including eGFR) • LFTs
8. Monitoring	<p>To be undertaken by secondary / tertiary care:</p> <ul style="list-style-type: none"> • Platelet count between day 5 to day 8 of treatment to monitor for heparin induced thrombocytopenia (HIT) • Creatinine and electrolytes between day 5 to day 8 of treatment in those patients at risk of hyperkaleamia • Platelet count repeated at 4 weeks <p>No routine monitoring is required in primary care.</p>
9. Pharmaceutical aspects	<p>Single dose syringes: Do not store above 25°C. Dalteparin pre-filled syringes are single dose containers - discard any unused product</p>
10. Secondary care contact information	<p>If stopping medication or needing advice please contact the referring clinician.</p> <p>Advice can be obtained at UHW from:</p> <ul style="list-style-type: none"> • Dr R Alikhan/Dr R Rayment 029 20742155 • or via UHW switchboard 029 2074 7747 <p>OR at Velindre from:</p> <ul style="list-style-type: none"> • Dr S Noble, Consultant, available on Monday mornings 02920 615888 ext 6225 (Out-patient reception) • or via Velindre Hospital switchboard 02920 615888
11. Criteria for shared care	<p>Prescribing responsibility will only be transferred when</p> <ul style="list-style-type: none"> • Treatment is for a specified indication and duration. • Treatment has been initiated and established by the secondary/tertiary care specialist • The patient's initial reaction to and progress on the drug is satisfactory. • The GP agrees to undertake SC when they receive SCP and SC request and the request form is sent back by the GP to the initiating centre indicating acceptance or not to take over SC responsibilities. The GP must also have received a handover letter from the consultant once the patient is stabilised • The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.

<p>12. Responsibilities of initiating consultant</p>	<ol style="list-style-type: none"> 1. To ensure the patient has a basic understanding of what risks and benefits are associated with dalteparin therapy, and to inform the patient of what action to take in the event adverse effects (particularly any unexplained bleeding). 2. To confirm the patient's understanding and consent to treatment 3. To undertake baseline investigations (see section 7 above) 4. To review and make recommendations about drugs affecting haemostasis that the patient may be taking (e.g. NSAIDs) 5. Initiate treatment with dalteparin providing the first 28 days of treatment and to inform the patient of the arrangements for obtaining further prescriptions. 6. Monitor for heparin-induced thrombocytopenia (HIT) by arranging and reviewing a platelet count between day 5 to day 8 of treatment 7. Monitor for hyperkalaemia in at-risk patients where this is needed by arranging and reviewing a potassium level between day 5 to day 8 of treatment 8. Educate the patient or carer on administration (or arrange for district nurse to be involved). 9. Initiate treatment with dalteparin and to inform the patient of the dose reduction from month 2 and inform the patient of arrangements for obtaining further prescriptions 10. To ensure patients presenting at Cardiff and Vale UHB with a subsequent diagnosis of a VTE and a solid tumour diagnosis where there is a need for extended treatment with dalteparin are referred to the Velindre cancer-associated thrombosis clinic for their 4 week follow up
<p>13. Responsibilities of Velindre cancer-associated thrombosis clinic</p>	<ol style="list-style-type: none"> 1. To send the shared care agreement form to the GP 2. When a GP positive response to the shared care has been received and patient has been stabilised send a letter to the GP "handing over" the shared care of the patient to the GP 3. Provide advice and support if problems occur during treatment using the contact details provided 4. Respond to any request from GP to review the patient due to adverse effects of therapy 5. Velindre consultant to keep patient under clinical review, assessing the need for ongoing dalteparin treatment before the 6 months treatment is completed. 6. Where the risk/benefit to the patient favours continuation beyond the licensed 6 month duration then, with the patient's acceptance, the patient

	<p>will be “handed back” to the Velindre consultant to prescribe the dalteparin.</p> <ol style="list-style-type: none"> 7. The Velindre consultant will write to the GP informing the GP the outcome of the clinical review and whether the treatment is stopping at 6 months (or before) or will continue with the prescribing responsibilities reverting to the Velindre consultant after the 6 months of treatment has been completed. 8. Give direction as to when treatment should be discontinued in all cases as appropriate, including those patients where treatment has continued beyond 6 months and where the prescribing responsibilities have reverted to the Velindre consultant. 9. To send confirmation letter to patient and/or carer when treatment is discontinued
<p>14. Responsibilities of primary care</p>	<ol style="list-style-type: none"> 1. To respond to the shared care agreement form (attached below). 2. To prescribe dalteparin in collaboration with the specialist and follow these guidelines. 3. Whenever practicable, to reaffirm with the patient the importance of reporting any unexplained bleeding. 4. To be aware of the increased risk of hyperkalaemia in those patients at higher risk of raised plasma potassium concentrations i.e .those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs 5. To discontinue treatment if patient is experiencing severe side effects and specialist advice is not immediately available. 6. To annotate the GP clinical computer system if the decision is made for the patient to continue to receive treatment of dalteparin beyond 6 months from the Velindre consultant and where prescribing responsibilities have reverted to the Velindre consultant
<p>15. Responsibilities of patients</p>	<ol style="list-style-type: none"> 1. To attend hospital and GP clinic appointments. 2. Failure to attend will result in medication being stopped on specialist advice. 3. To report adverse effects to their specialist or GP (particularly any unexplained bleeding)
<p>16. Additional Responsibilities</p>	<p>Responsibilities of all prescribers: As dalteparin is a black triangle drug (▼) all suspected adverse reactions (including those not considered to be serious) should be reported to CHM/MHRA via the “yellow card scheme.” http://yellowcard.mhra.gov.uk/</p>

17. Supporting documentation / information	<p>Other information: NPSA/2010/RRR014 states: <i>Essential information such as dose, weight, renal function, indication and duration of treatment is communicated at transfers of care (e.g. by discharge letters) and used to ensure that future doses are safe.</i> http://www.nrls.npsa.nhs.uk/resources/?entryid45=75208</p> <p>In 2010 (April & December) the All Wales Medicines Strategy Group (AWMSG) considered issues relating to LMWH and has produced documents to promote uptake of best practice and to reduce avoidable harm, waste and variation in NHS Wales: http://www.wales.nhs.uk/sites3/page.cfm?orgid=371&pid=46618</p> <p>Patient information leaflet http://emc.medicines.org.uk/medicine/14282/PIL/Fragmin%2010000.%2012500.%2015000.%2018,000%20I.U%20Syringes/</p>
18. Patient Monitoring Booklet	Not needed
19. GP letter	Attached below
20. Guideline date.	December 2013
21. Guideline review date	December 2015

References

1. Lyman G.H., et al, 2007. American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer. *Journal of Clinical Oncology*, 25 (34), pp.5490-5505.
[\[http://jco.ascopubs.org/cgi/content/abstract/JCO.2007.14.1283v1\]](http://jco.ascopubs.org/cgi/content/abstract/JCO.2007.14.1283v1)
2. Expert opinion provided by Chris Gorman (Consultant Ophthalmologist, Cardiff and Vale NHS Trust), Carol Lane (Ocular Plastic Consultant, Cardiff and Vale NHS Trust) Chris Williams (Consultant Ophthalmologist, Cardiff and Vale NHS Trust), Graham Roblin (ENT Consultant, Cardiff and Vale NHS Trust)

Shared care agreement – next page

Shared Care Agreement Form

CONSULTANT REQUEST

To: Dr.

Your patient:	NHS No. (10digit):
was seen on:	
with a diagnosis of:	
I have initiated:	

This drug has been accepted as suitable for shared care by the Bro-Taf D+T Committee and C+V MMG. I agree to the responsibilities set out in the protocol SCP No. _____ (*copy attached*). This should be read in conjunction with the general guidance for shared care prescribing

I am requesting your agreement to sharing the care of this patient. The preliminary tests set out in the protocol have been carried out. I am currently prescribing the stabilising treatment.

I would like you to undertake treatment from:
The required dose from this date onwards will be:

If you undertake treatment I will reassess the patient in ____ weeks. You will be sent a written summary within 14 days. I will accept referral for reassessment at your request.

The medical staffs of the department are available at all times to give you advice.

Consultant Name:	Signature:
Department:	
Hospital:	Date:
Contact Telephone No's:	

GP RESPONSE

Dear Dr

Patient *(Insert Patients name)*

Identifier *(Insert Patient Date of Birth/address)*

I have received your request for Shared Care of this patient who has been initiated on Dalteparin

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient because (please state reason)

GP signature

Date

GP address/practice stamp

**PLEASE RETURN WHOLE COMPLETED FORM OR A COPY TO THE REQUESTING CONSULTANT
WITHIN ONE WEEK**

CONSULTANT CONFIRMATION

Letter to GP - to confirm patient is stable on shared care drug

Do not send unless GP has returned the Shared Care request form and has accepted Shared Care for this patient

Date

To Dr.

Name of patient..... (attach addressograph)

Diagnosis: **Venous thromboembolism in patients with solid tumours**

Drug name: **Dalteparin** Dose:units s/c once daily

Any further patient details (if necessary)

Thank you for agreeing to undertake **shared care** for the above patient. He/she is now stable.

Please will you arrange for dalteparin to be added to the patient's repeat prescription. Treatment will be continued for up to six months. The first months of dalteparin treatment has been prescribed and issued by secondary care.

I will review the patient before the six month treatment has been completed and make the decision as to whether there is a continued need for treatment.

If there are any problems relating to the care of this patient in the meantime please contact

Name.....

Telephone number.....