Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

dalteparin sodium, 5,000IU/0.2mL, 7,500IU/0.3mL, 10,000IU/0.4mL, 12,500IU/0.5mL, 15,000IU/0.6mL, 18,000IU/0.72mL solution for injection. (Fragmin®) SMC No. (683/11)

Pfizer Ltd.

04 February 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dalteparin (Fragmin®) is accepted for restricted use within NHS Scotland.

Indication under review: extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence in patients with solid tumours.

SMC restriction: initiation by healthcare professionals experienced in the treatment of VTE.

In patients with cancer and VTE, dalteparin significantly reduced the rates of VTE recurrence over a six month period, compared to oral anticoagulation. Bleeding and mortality rates for patients receiving dalteparin were similar to those reported in patients receiving oral anticoagulant.

The economic case was demonstrated for dalteparin compared to other low molecular weight heparins.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence in patients with solid tumours.

Dosing Information

Dalteparin is administered by subcutaneous injection once daily at a dose of 200IU/kg total body weight (dose banded from 7,500IU to maximum 18,000IU) for the first 30 days followed by a daily dose of approximately 150IU/kg (dose banded from 7,500IU to a maximum 18,000IU) during months two to six. Dose adjustment is required in cases of significant renal failure or chemotherapy-induced thrombocytopenia; dose adjusted to anti-factor Xa activity in renal failure; dose reduced by 2,500IU/day when platelet counts between 50,000 and 100,000/mm^3; and discontinuation of dalteparin in patients with platelet counts below 50,000/mm^3 until recovery above this level.

Product availability date

Licence extension 5 May 2009

Summary of evidence on comparative efficacy

Dalteparin sodium is a low molecular weight heparin (LMWH). Its antithrombotic properties are mediated by its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time. Dalteparin is an established anticoagulant for the treatment of several anti-thrombotic indications; this is a new indication covering extended treatment of venous thromboembolism (VTE) in patients with solid tumours.

Evidence for this indication comes from a multinational, multicentre, randomised, open-label, comparative, six-month clinical study to determine whether dalteparin was more effective and safer than oral anticoagulant therapy in preventing recurrent thromboembolism in patients with cancer who had acute VTE. Patients eligible for inclusion in the study had active cancer, with the exception of basal- or squamous-cell skin cancer, and newly diagnosed symptomatic proximal deep-vein thrombosis and/or pulmonary embolism, and were randomised to one of two treatment groups: dalteparin, or oral anticoagulation with warfarin or acenocoumarol.

Patients assigned to the dalteparin group received dalteparin 200 international units/kg/day, up to a maximum of 18,000 international units, for the first month (administered from multi-dose vials). Pre-filled syringes were used to administer the dose for months two to six, which was approximately 150 international units/kg/day, dose banded by weight as follows; patients 40 to 56kg in weight were given 7,500 international units/day; patients weighing 57 to 68kg were given 10,000 international units; patients weighing 69 to 82kg received 12,500 international units; patients weighing 83 to 98kg were given 15,000 international units; while patients over 99kg received a daily dose of 18,000 international units. Dose adjustment was made (according to anti-Factor Xa activity) if there was significant renal impairment.

Patients assigned to the oral anticoagulant arm were given dalteparin 200 international units/kg/day while the oral anticoagulant was titrated to a target international normalised ratio (INR) of 2.5 (range 2.0 to 3.0). Dalteparin was discontinued after at least five days and once the INR was greater than 2.0 on two consecutive days. The INR was subsequently monitored at least once a fortnight.

Dosage in both arms was reduced in the presence of mild thrombocytopenia (platelet count 50-99x10^3/mm^3); dalteparin was reduced by 2,500IU/day; and patients in the oral anticoagulant group had a reduced target INR of 2.0 (range 1.5 to 2.5). Both oral anticoagulant and dalteparin were withheld if platelet count was less than 50x10^3/mm^3 until it was greater than 100x10^3/mm^3.

The primary endpoint for the study was the first episode of an objectively diagnosed, symptomatic, recurrent venous thromboembolic event: deep vein thrombosis or pulmonary embolism during the six-month period of follow-up. Rates of recurrent VTE are presented in Table 1.

	Dalteparin treatment group (n=336)		Oral anticoagulant treatment group (n=336)	
	No. of patients	Proportion	No. of patients	Proportion
Deep vein thrombosis alone	14	4.2%	37	11%
Non-fatal pulmonary embolism	8	2.4%	9	2.7%
Fatal pulmonary embolism	5	1.5%	7	2.1%
Total recurrent VTE	**27**	**8.0%**	**53**	**16%**

Table 1: Recurrence rates of venous thromboembolism.

Based on the results of this study, there was a significant difference in the rate of VTE recurrence between the two groups in favour of dalteparin, and for every 13 cancer patients with an episode of VTE who received 6 months of dalteparin instead of an oral anticoagulant there was 1 fewer recurrent episode of VTE. The hazard ratio for recurrent VTE over the six-month period for the dalteparin group compared to oral anticoagulation was 0.48 (95% confidence interval [CI] 0.3 to 0.77). At six-months the probability of VTE recurrence, estimated using the Kaplan-Meier method, for dalteparin was 9% and 17% in the oral anticoagulant group, a significant difference.

There was no statistical difference in mortality rates between the groups; dalteparin 39% (n=130/336); and oral anticoagulants 41% (n=136/336). Of these 266 deaths, 90% were attributed to cancer progression.

Summary of evidence on comparative safety

Adverse events observed with dalteparin are mostly related to the anticoagulant effects of the medicine; haemorrhage at any site and subcutaneous haematoma at the site of administration. Dalteparin is associated with a mild thrombocytopenia, and rarely an immunologically-mediated heparin-induced thrombocytopenia.

Bleeding events were considered secondary outcomes in the study comparing dalteparin with oral anticoagulants. Overall bleeding rates were similar between the two groups, 14% (47/338) for dalteparin, and 19% (64/335) for patients in the oral anticoagulant group. A major bleeding event was defined as one that: was associated with death; occurred at a significant site, e.g.

intraspinal, intraocular, pericardial, intracranial, retroperineal; resulted in a drop in haemoglobin of at least 20g/L; or required the patient to have at least 2 units of blood transfused. Major bleeding occurred in 5.6% (19/338) of patients treated with dalteparin, which was similar to the rates of major bleeding in the oral anticoagulant group, 3.6% (12/335). Major bleeding was associated with thrombocytopenia in two patients in the dalteparin group and an elevated INR (>3.0) in the oral anticoagulant group. In the dalteparin group, there were three patients who bled at a critical site; one intracranial bleed in a patient with a brain tumour; one retroperitoneal bleed in a patient with prostate cancer; and a patient with lung cancer experienced a pericardial bleed. One patient treated with dalteparin had a fatal bleeding event which was a massive haemoptysis in the background of metastatic lung cancer. There was no fatal bleeding event in the oral anticoagulant group and four patients experiencing bleeding events at a critical site; two patients experienced intracranial bleeds, one patient had breast cancer, and the other had prostate cancer; and two patients had a retroperitoneal bleed, one with a brain tumour and one with prostate cancer.

Summary of clinical effectiveness issues

The study utilised an open label design due to concerns of potential drug interactions in patients randomised to oral anticoagulants. Risk of bias from this design was minimised by the use of objective measures for treatment outcomes and investigators blinded to treatment allocation were used to adjudicate any suspected events. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, therefore evidence of efficacy is limited to this fitter patient group . According to treatment guidelines, the current standard of care for the treatment of VTE in patients with cancer is the use of LMWH. This is reflected by comments from SMC experts although there is some use of warfarin in current practice. The comparator used in this study was oral anticoagulants, which were the treatment of choice at the time the study was carried out. In fact, this study is a key reference for treatment guidelines. There are no direct comparative studies between dalteparin and any other LMWH, and an indirect comparison was not presented due to the lack of a common comparator. A mixed treatment comparison may have been possible, but due to the limited number of identified studies, the usefulness of odds ratios would be diminished by wide confidence intervals.

Most of the documented difference in efficacy between dalteparin and oral anticoagulants is in the prevention of recurrent deep venous thrombosis rather than in the prevention of the more serious manifestations of VTE.

There are some potential advantages with the use of dalteparin for the service and for the patient. Currently, dalteparin is the only LMWH in the UK with a marketing authorisation specifically for the extended treatment of patients with cancer diagnosed with a VTE so there is clear dosing advice for this patient group to aid prescribers. The dose of dalteparin is banded to full pre-filled syringes, so there is no requirement to administer part of a syringe, reducing the complexity of administration for patients or their carers. The use of LMWH avoids the known complications of oral anticoagulants such as warfarin, in patients with cancer. A key issue is that warfarin has variable pharmacokinetics which are affected by conditions commonly experienced by cancer patients such as vomiting, diarrhoea, malnutrition and liver impairment.

Summary of comparative health economic evidence

The manufacturer presented a simple cost-minimisation analysis comparing dalteparin with enoxaparin or tinzaparin for the extended treatment of symptomatic VTE in patients with solid tumours. The analysis was conducted over a 6 month time horizon. Expert responses indicated the comparators used were appropriate as LMWHs are already used for the extended treatment of VTE in patients with cancer. Comparable efficacy of dalteparin and the other LMWHs, which underpins the use of a cost-minimisation analysis, was based on assumption only. Only drug acquisition costs were included, which seems appropriate.

The results of the analysis indicated that dalteparin would be associated with cost savings over the six month time period of between £370 and £450 per patient compared to enoxaparin and between £730 and £1,180 per patient compared to tinzaparin. The range of savings reflected the different drug costs according to patient weight.

The following weaknesses were noted:

- A key weakness is the lack of available data comparing the efficacy of dalteparin with other LMWHs. However, it should be noted that neither tinzaparin nor enoxaparin is licensed for this indication.
- An indirect comparison to support the assumption of comparable efficacy of dalteparin and the other LMWHs, as required to justify the cost-minimisation analysis, was not conducted. However, the manufacturer claimed that this is a conservative assumption as dalteparin is the only LMWH which has shown a statistically significant reduction in recurrent VTE in cancer patients compared to standard anticoagulant therapy.
- Warfarin is used as a treatment in a small group of patients but no analysis was presented to show the cost-effectiveness compared to warfarin,

Despite these weaknesses, the cost-minimisation analysis shows that dalteparin is the least expensive LMWH and therefore the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published its SIGN Guideline 122 "Prevention and management of venous thromboembolism" in 2010. In section 12.1, the current recommendation is that LMWH rather than warfarin should be considered in VTE associated with cancer.

In 2008 The Association of Palliative Medicine for Great Britain and Ireland published a paper, "Management of venous thromboembolism in patients with advanced cancer: a systematic review and meta-analysis". The recommendations made included; for the long-term secondary prophylaxis of venous thromboembolism in patients with cancer at any stage, performance

status, or prognosis, full-dose LMWH should be the drug of choice; patients should remain on anticoagulation for at least 6 months after the first episode, although indefinite anticoagulation should be considered.

The European Society of Cardiology published "Guidelines on the diagnosis and management of acute pulmonary embolism" in 2008. They recommend that for the treatment of pulmonary thromboembolism in patients with cancer, LMWH should be considered for the first three to six months and anticoagulant treatment should be continued indefinitely or until definitive cure of the cancer.

The American Society of Clinical Oncology produced guidelines in 2007 detailing their "Recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer". On the subject of patients with cancer and established VTE; LMWH is the preferred option for the initial five to ten days of anticoagulant treatment and for the proceeding six months. If LMWH is not available, then a vitamin K antagonist, e.g. warfarin, with a target INR of 2 to 3 is acceptable. Indefinite anticoagulant therapy should be considered in selected patients with active cancer, after the six month treatment time.

Additional information: comparators

Comparators include the oral anticoagulants (warfarin, acenocoumarol, and phenindione) and several parenteral anti-coagulants used in the treatment of VTE: bemiparin, enoxaparin, fondaparinux, and tinzaparin. All the parenteral agents are licensed for the initial treatment of VTE until adequate oral anticoagulation is established, thus extended treatment in patients with cancer is off-label.

Cost of relevant comparators

Drug	Dose Regimen	Cost per six month (180 day) course (£)*
Dalteparin	**Subcutaneous injection: 200IU/kg daily for one month, then 150IU/kg daily for five months.**	**1,313**
Tinzaparin[≠]	175IU/kg by subcutaneous injection once daily	2,133
Fondaparinux[≠]	Subcutaneous injection as per bodyweight daily <50kg: 5mg, 50-100kg: 7.5mg, >100kg: 10mg	2,098
Enoxaparin[≠]	1.5mg/kg by subcutaneous injection once daily	1,759
Bemiparin[≠]	115units/kg by subcutaneous injection once daily	789
Warfarin	Adjusted to target INR of 2.5 (range 2 to 3)	8[#]

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 24 November 2010.

* Costs for weight-based doses are calculated based on a patient weighing 70kg, and use of pre-filled syringes.

[≠] Tinzaparin, fondaparinux, enoxaparin, and bemiparin are unlicensed for extended use following VTE and the dose regimens used are based on the dosage recommended for the initial treatment of VTE while oral anticoagulation is established.

[#] Cost based on WHO defined daily dose of 7.5mg.

Additional information: budget impact

The manufacturer estimated the net budget impact would be £8k in year 1 rising to £41k in year 5. These estimates are only based on the increased costs resulting from an increase in prevalence rates and more patients being treated with dalteparin as a result. The gross drug budget impact of all patients treated with dalteparin was estimated to be £328k in year 1 rising to £361k in year 5. These estimates assume a constant market share of 50.5% which results in 293 patients in year 1 and 323 in year 5.

If dalteparin replaces all other LMWH use over the next 5 years, the manufacturer estimated this would result in an initial cost of £8k in year 1 and a cost saving of £55k by year 5. Estimated patient numbers were 293 in year 1 (50.5% market share) and 519 in year 5 (81% market share).

If dalteparin replaces all other LMWH use and warfarin use over the next 5 years, the manufacturer estimated this would result in an initial cost of £8k in year 1 rising to £72k in year 5. Estimated patient numbers for this analysis were 293 in year 1 (50.5% market share) and 639 in year 5 (100% market share). This estimate assumes that all patients self-inject. Increased administration costs may result if existing warfarin patients move to dalteparin and are unable to self-inject.

References

The undernoted reference was supplied with the submission.

Lee AY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003 Jul 10; 349(2): 146-53.

This assessment is based on data submitted by the applicant company up to and including 14 January 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.