

In Confidence

tinzaparin 20,000 IU/ml 0.4ml, 0.5ml, 0.6ml, 0.7ml, 0.8ml and 0.9ml pre-filled syringe (Innohep Syringe[®]) SMC No. (1061/15)

Leo Pharma

05 June 2015

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

tinzaparin (Innohep Syringe[®]) is accepted for use within NHS Scotland.

Indication under review: Patients with solid tumours: Extended treatment of symptomatic venous thrombo-embolism (VTE) and prevention of its recurrence.

In patients with cancer and VTE, tinzaparin was associated with rates of VTE recurrence that were not significantly different from those with a vitamin K antagonist (VKA). In a large study it was not significantly different from a VKA for a composite outcome that included symptomatic deep vein thrombosis (DVT), non-fatal and fatal pulmonary embolism (PE), incidental DVT and PE.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tinzaparin. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Patients with solid tumours: Extended treatment of symptomatic venous thrombo-embolism and prevention of its recurrence.

Dosing Information

175 IU/kg by subcutaneous injection once daily for six months.

Product availability date

23 December 2014

Summary of evidence on comparative efficacy

Tinzaparin is a low molecular weight heparin (LMWH) that has a new indication for use in patients with solid tumours, as extended treatment of symptomatic venous thrombo-embolism (VTE) and prevention of its recurrence.¹

An open-label study (MainLITE-cancer) recruited 200 adults with cancer and venography or ultrasound confirmed acute proximal-vein thrombosis. Randomisation was stratified by study centre, primary or recurrent venous thrombosis and high or low risk of bleeding. Patients were equally assigned to 12 weeks treatment with tinzaparin 175 IU/kg subcutaneous (SC) injection once daily or unfractionated heparin intravenous (IV) infusion for six days that overlapped with warfarin adjusted to achieve an international normalised ratio (INR) of 2 to 3. Therapy could be continued after 12 weeks if oral anticoagulation was indicated as determined by the physician. The primary outcome was rate of objectively documented VTE or death at 12 weeks confirmed by an independent blinded central adjudication committee. At 12 weeks, 6% (6/100) and 10% (10/100) of patients in the tinzaparin and heparin-warfarin groups, respectively, had a recurrent VTE, with a between group difference of -4.0% (95% confidence interval (CI): -12.0% to 4.1%). In the respective groups, similar numbers of patients had died: 20% (20/100) and 19% (19/100), difference of 1.0% (95% CI: -10.2% to 11.9%). At 12 months, 7% (7/100) and 16% (16/100) of patients, respectively, had a recurrent VTE, with a difference of -9.0% (95% CI: -21.7% to -0.7%); and 47% (47/100) of patients in each group had died.²

In an open-label study conducted at two centres in Spain, 241 adults with ultrasound confirmed first episode of acute proximal-vein thrombosis of the lower limbs were given tinzaparin 175 IU/kg SC injection once daily. They were randomised to continue this for six months or to commence six months of acenocoumarol treatment and discontinue tinzaparin when an INR between 2 and 3 was achieved. The primary outcome was objectively confirmed DVT or PE at six months and one year. The study included a subgroup of patients with cancer: 36 and 33 patients in the tinzaparin and acenocoumarol groups, respectively. In this subgroup, 5.5% (2/36) and 9.1% (3/33) of patients had a recurrent VTE, at 6 months, and 5.5% (2/36) and 21.2% (7/33), respectively, at one year. The differences between the groups were not significant.³

An open-label phase III study (CATCH) recruited 900 adults with active cancer (histologically or cytologically confirmed solid tumour or a haematological malignancy), symptomatic objectively confirmed DVT and/or PE and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2 prior to VTE. Randomisation was stratified by tumour (distant metastasis, no distant metastasis or haematological malignancy), geographical region and previous VTE (yes or no). Patients were equally assigned to tinzaparin 175 IU/kg SC once daily for six months or this dose of

tinzaparin for 5 to 10 days, overlapping with warfarin adjusted to achieve INR of 2 to 3 for six months. The primary composite outcome was time to first occurrence up to six months of any of the following objectively confirmed events validated by a blinded independent central committee: symptomatic DVT, symptomatic non-fatal PE, fatal PE, incidental proximal DVT (popliteal vein or higher) or incidental proximal PE (segmental arteries or larger).⁴ Over the six-month study period, 6.9% (31/449) and 10% (45/451) patients in the tinzaparin and warfarin groups, respectively, experienced a recurrent VTE (i.e. the composite primary outcome), with a hazard ratio (HR) of 0.65 (95% CI: 0.41 to 1.03, $p=0.07$). Symptomatic non-fatal DVT occurred in 2.7% (12/449) and 5.3% (24/251) of patients, respectively, HR 0.48 (95% CI: 0.24 to 0.96), $p=0.04$. Symptomatic non-fatal PE occurred in 3 and 2 patients, respectively. In the respective groups, fatal PE occurred in 3.8% (17/449) and 3.8% (17/451) of patients, HR 0.96 (95% CI: 0.49 to 1.88). Incidental VTE occurred in 2 patients in the warfarin group. Overall survival rate at six months was 59% and 60%, respectively.⁵

Summary of evidence on comparative safety

The adverse event profile of tinzaparin is well characterised and consistent with that of LMWHs. One of the main adverse effects of anticoagulation is bleeding.

In the MainLITE-cancer study, major bleeding was defined as overt and associated with a fall in the haemoglobin (Hb) of at least 2g/dL, transfusion of at least 2 units, or was intracranial, retroperitoneal, or into a major joint. Minor bleeding was clinically overt, but did not meet other criteria for major bleeding. In the MainLITE-cancer study at 3 months within the respective tinzaparin and heparin-warfarin groups, 27% (27/100) and 24% (24/100) of patients had experienced a bleed, with 7% of patients in both groups having a major bleed. Minor bleeds were reported by 20% and 17% of patients in the respective groups. The differences between the groups for all, major and minor bleeds were not statistically significant.²

In the CATCH study, major bleeding was defined as overt and associated with a fall in Hb of at least 2g/dL, transfusion of at least 2 units, or was intracranial, intraspinal, intraocular, pericardial, retroperitoneal or associated with death. Major bleeding events occurred in 2.9% (13/449) and 2.7% (12/451) of patients in the tinzaparin and warfarin groups, respectively. Clinically relevant non-major bleeding was reported by 11% (50/449) and 16% (73/451) of patients in the respective groups, $p=0.03$.⁵

Summary of clinical effectiveness issues

Tinzaparin is the second LMWH (after dalteparin) licensed in the UK for extended treatment of symptomatic VTE and prevention of its recurrence in patients with solid tumours. In March 2011, SMC issued advice that dalteparin was accepted for restricted use in this indication. The restriction was to initiation by healthcare professionals experienced in the treatment of VTE.

In each study, the primary outcomes were objectively confirmed and adjudicated by central blinded independent committees but they differed across the studies²⁻⁵. In MainLITE-cancer, the primary outcome was symptomatic VTE or death, and in the Spanish study, it was symptomatic VTE. There was no significant difference between the tinzaparin group and the VKA group for the primary outcomes in these analyses but they may have been underpowered to detect a clinically relevant difference between treatment groups. In the CATCH study, the primary outcome was a composite of five events (symptomatic DVT, non-fatal PE, fatal PE, incidental DVT, and incidental PE). This was not significantly different with tinzaparin compared to warfarin. However, the secondary outcome of symptomatic DVT occurred at a significantly reduced rate with tinzaparin.

In the MainLITE-cancer study, oral anticoagulation could be continued or commenced after anticoagulation with study treatment stopped at 3 months at the discretion of the primary care physician. There was an imbalance between the tinzaparin and warfarin groups in the proportions of patients who received oral anticoagulation after 3 months: 37% (37/100) and 57% (57/100), respectively. This would not impact the rate of VTE recurrence at 3 months (primary outcome), but could bias the assessment of VTE recurrence at 12 months.

The Spanish and MainLITE-cancer studies excluded patients with PE requiring thrombolysis, thrombectomy or vena cava interruption. This may limit the generalisation of results from these studies to this group of patients in practice.

The comparator in the Spanish study was acenocoumarol, an anticoagulant not commonly prescribed within NHS Scotland. However, it was titrated to achieve an INR of 2 to 3, which is the target range for oral VKA anti-coagulants within Scottish practice. Scottish Intercollegiate Guidelines Network (SIGN) guideline number 122 on the prevention and management of VTE recommends that LMWH, rather than warfarin, should be used for VTE in patients with cancer. Scottish clinical experts consulted by SMC confirmed this. Therefore, the comparators in all three studies were not reflective of Scottish practice. The only other LMWH that has been licensed for extended treatment of VTE in patients with cancer is dalteparin. There were no direct comparative data for tinzaparin and dalteparin in this indication.

Adjusted pair-wise comparisons of tinzaparin and dalteparin were undertaken in patients with VTE and cancer for the outcomes of recurrence of VTE and major bleeding. The base case included four studies and a further study was included in a sensitivity analyses. From the results it was concluded that the treatments were similar. This indirect comparison was limited by several weaknesses including inclusion of a small study in patients without cancer and exclusion of a large study relevant to the comparison. However, sensitivity analyses provided reassurance with respect to these. There were insufficient data to adequately compare baseline risk of recurrent VTE across the studies. Heterogeneity across the studies was noted in terms of initial anticoagulant (LMWH or unfractionated heparin), comparator (warfarin or acenocoumarol) and duration of anticoagulant treatment (3 to 6 months). There was also heterogeneity in duration (6 to 12 months) and type of assessments during follow-up for VTE and some variation in definitions of this. There were differences across the studies in rates of outcomes observed in the common control, VKA treatment groups.

Tinzaparin may provide an advantage over dalteparin as there is no requirement for dose adjustment of tinzaparin after 1 month of treatment. Clinical experts consulted by SMC note that dose adjustment with dalteparin does not occur in every patient. In addition, dalteparin requires dose adjustment in patients with renal impairment where creatinine clearance is less than 30 ml/min, but the Summary of Product Characteristics for tinzaparin notes that available evidence suggests that no dose reduction is needed in patients with creatinine clearance levels down to 20 ml/min.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing tinzaparin to dalteparin for the extended treatment of symptomatic VTE and prevention of its recurrence in patients with solid tumours. Dalteparin was confirmed by SMC clinical experts as an appropriate comparator. A six month time horizon was adopted.

The clinical evidence used to support the cost-minimisation analysis was the indirect comparison referred to in the clinical effectiveness section, which concluded that the treatments had similar

effectiveness. The submitting company also presented a cost-utility analysis using the non-significant differences from the indirect comparison but the use of the cost-minimisation analysis as the base case seemed appropriate.

Costs in the analysis related to the drug acquisition costs of the medicines and any associated clinician visits related to dose reductions. For dalteparin, the company assumed that not all patients in clinical practice would have their dose reduced after the first month of treatment; instead it was assumed that only 48% of patients would have dose reductions and for these patients a clinician visit would be required. No dose reductions or clinician visits were assumed for tinzaparin.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of the medicine.

The results of the analysis without the PAS are shown below, based on a weighted average across patient weights:

	Drug costs £	Resource use costs £	Total costs £	Incremental costs associated with tinzaparin £
Without PAS				
Dalteparin	1366	33	1399	
Tinzaparin	1470	-	1470	71

With the PAS, tinzaparin became a cost-effective treatment option.

Sensitivity analysis tested the assumptions on patient weight, % of patients requiring dose reduction with dalteparin and the use of clinician visits for dose reductions. The results indicated that tinzaparin generally remained cost-effective with the PAS except as follows:

- Tinzaparin was not cost-effective if all patients on dalteparin had dose reductions, or if 100% or 75% of patients on dalteparin had dose reductions but these were not associated with a health care visit.
- At patient weights below 69kg, tinzaparin would not be cost-effective if all patients on dalteparin were assumed to have dose reductions (and dose reductions all required an HCP visit).
- Under the scenario which was most conservative (all patients on dalteparin had dose reductions and there was no additional visit associated with them), tinzaparin would not be cost-minimising at weights below 83kg.

In terms of weaknesses, the cost-minimisation analysis was based on the outputs of an indirect comparison. As noted above, this analysis had weaknesses which introduced uncertainty to the economic evaluation but the additional sensitivity analysis from the company on the indirect comparison provided some reassurance.

SMC clinical experts were asked for their views about the assumptions made, particularly concerning dose reduction for dalteparin. The responses were mixed, but indicated that such dose reductions are not always made in clinical practice and, therefore, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from AntiCoagulation Europe and Thrombosis UK, both registered charities.
- Both AntiCoagulation Europe and Thrombosis UK have received pharmaceutical company funding in the past two years, with AntiCoagulation Europe having received funding from the submitting company.
- Cancer associated thrombosis (CAT) is a serious medical complication of cancer and can cause additional stress, anxiety and discomfort when managing the symptoms. For patients already coping with a cancer diagnosis, the additional stress of having a CAT is devastating. Fear of developing further, possibly lethal clots is difficult to cope with. The availability of safe and effective treatments for patients can help patients to come to terms with their condition.
- Patients with CAT are often treated with LMWH to prevent further VTE episodes. Tinzaparin would provide clinicians and patients with another LMWH option that would allow treatment to be tailored to individual patients.
- Tinzaparin is a treatment that appears to be safe to use for the extended treatment of symptomatic VTE and recurrence in patients with solid tumours. A second LMWH treatment will give patients who cannot tolerate dalteparin, another option.

Additional information: guidelines and protocols

In December 2010 SIGN published guideline number 122 on the prevention and management of VTE. This recommends that LMWH rather than warfarin should be considered in VTE associated with cancer.⁶

In 2011 the European Society for Medical Oncology (ESMO) published clinical practice guidelines for the management of VTE in cancer patients. These note that the standard initial treatment of an acute episode of VTE in cancer and non-cancer patients consists of SC LMWH or unfractionated heparin intravenously in a continuous infusion adjusted to achieve and maintain an activated partial thromboplastin time (aPTT) prolongation of 1.5–2.5 times the basal value. The results of studies of the LMWH heparins (dalteparin, enoxaparin and tinzaparin) versus VKA in patients with VTE and cancer are detailed. It is noted that the results from all these clinical trials demonstrate that in these patients long-term treatment for 6 months with 75% to 80% of the initial dose of LMWH is safe and more effective than treatment with a VKA. This schedule is recommended for long-term anticoagulant therapy in cancer patients.⁷

In 2014 the European Society for Cardiology (ESC) published Guidelines on the diagnosis and management of acute pulmonary embolism. These note that when selecting the mode of anticoagulation in patients with cancer and acute PE, LMWH administered in the acute phase (except for high-risk PE) and continued over the first 3 to 6 months should be considered as first-line therapy. Chronic anticoagulation may consist of continuation of LMWH, transition to VKA, or discontinuation of anticoagulation. The decisions should be made on a case-by-case basis after considering the success of anti-cancer therapy, the estimated risk of recurrence of VTE, the bleeding risk, and the preference

of the patient. Periodic reassessment of the risk–benefit ratio of chronic anticoagulant treatment is a reasonable strategy.⁸

Additional information: comparators

The relevant comparator is the other LMWH licensed for this indication, dalteparin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Tinzaparin	175 IU/kg SC once daily for 6 months	1,300
Dalteparin	200 IU/kg SC once daily for 1 month, then 150 IU/kg SC once daily for 5 months	1,329

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 03 March 2015 and are based on a weight of 70kg. The costs do not take any patient access schemes into consideration

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 8,272 patients in year 1 rising to 13,231 in year 5. Confidential estimates of treatment uptake were then applied to these patient numbers.

Without PAS

The impact on the medicines budget was estimated at £1.59m in year 1 and £2.58m in year 5. The net medicines budget impact was estimated at £83k and £135k.

These estimates assumed that dose-reductions would occur with dalteparin as per the assumptions used in the economic analysis.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Leo Pharma. Summary of product characteristics for Innohep Syringe, accessed 10.03.15
2. Hull RD, Pineo GF, Brant RF et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006; 119(12): 1062-72.
3. Romera A, Cairols MA, Vila-Coll R et al. A randomised open-label trial comparing long-term subcutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg*. 2009 ; 37(3): 349-56.
4. Lee AY, Bauersachs R, Janas MS et al. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. *BMC Cancer* 2013, 13:284
5. Lee AC, Kamphuisen P W, Meyer G et al. A randomized trial of long-term tinzaparin, a low molecular weight heparin (LMWH), versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients - the CATCH study. Presented at the 56th American Society of Hematology Annual Meeting and Exposition, December 6-9, San Francisco, CA. 2014.
6. Scottish Intercollegiate Guidelines Network (SIGN) guideline number 122; prevention and management of venous thromboembolism, March 2010.
7. Mandala M, Falanga A, Roila A et al. European Society for Medical Oncology (ESMO) published clinical practice guidelines for the management of VTE in cancer patients. *Ann Oncol* 2011; 222 (suppl 6): vi85-vi92.
8. Konstantinides SV, Torbicki A, Agnelli G et al. 2014 ESC guideline on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35: 3033-73.

This assessment is based on data submitted by the applicant company up to and including 15 May 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately

from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.