AWMSG Secretariat Assessment Report – Limited submission

Tinzaparin sodium (innohep® Syringe) 20,000 units/ml solution for injection

Company: LEO Pharma

Licensed indication under consideration:
Adult patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.

Marketing authorisation date: 18 December 2014

Comparator(s):

- Dalteparin sodium (Fragmin®) – licensed indication
- Enoxaparin sodium (Clexane®) –off label use

Limited submission details:

The limited submission criteria were met as the anticipated usage in NHS Wales is considered to be of minimal budgetary impact and there is an estimated small difference in cost compared to comparators.

Clinical effectiveness:

- Three relevant studies were included in the submission: MainLITE Cancer (tinzaparin vs. usual care (short-term unfractionated heparin and long term warfarin), Romera 2009 (six months tinzaparin sodium vs. short term tinzaparin sodium plus acenocoumarol) and CATCH (six months tinzaparin vs. six months warfarin).
- At three months, results of the MainLITE Cancer trial showed a non statistically significant reduction of new episodes of venous thromboembolism (VTE) in the tinzaparin sodium treatment group (6% of patients) compared with those in the usual care group (10% of patients). At 12 months, statistically significantly fewer patients in the tinzaparin sodium group (7% of patients) had experienced VTE recurrence compared with the usual care group (16% of patients).
- In the Romera 2009 study, at 12 months, fewer patients in the tinzaparin sodium group had new episodes of VTE compared with the tinzaparin sodium followed by vitamin K antagonist (VKA) group: 5.5% (2/36) versus 21.2% (7/33) Acenocoumarol is a VKA which is rarely used in Wales when compared with warfarin.
- Results from CATCH have recently been published. Overall there were no statistically significant differences between the treatment arms for VTE recurrence, incidence of major bleeds or mortality rates. Tinzaparin was associated with a significant reduction in clinically relevant non-major bleeds when compared to warfarin.
- The comparators included in the trials are not reflective of current VTE

treatment guidelines for adults with solid tumours which recommend that low molecular weight heparins (LMWHs) are used for six months.

- In the absence of head-to-head trials comparing tinzaparin sodium with dalteparin sodium and enoxaparin sodium, the company has conducted a pairwise meta-analysis and indirect treatment comparisons (ITCs). Tinzaparin sodium was associated with numerically, but not statistically, reduced risks of VTE recurrence compared with dalteparin sodium and enoxaparin sodium. The studies included were heterogenous in terms of initial anticoagulant used, choice of VKA, duration of therapy, study duration, cancer type and assessed outcomes.
- No significant difference between treatment groups in terms of major bleeding was demonstrated in any of the trials or ITCs.
- Tinzaparin sodium does not require a dosage adjustment after one month unlike dalteparin sodium.
- The company state that for patients with renal insufficiency, tinzaparin sodium may provide a more convenient treatment option than dalteparin sodium or enoxaparin sodium due to the reduced likelihood that dose adjustment will be necessary. For tinzaparin sodium, the company state that available evidence suggests that no dose reduction is needed in patients with creatinine clearance levels down to 20 ml/min.

Budget impact:

- The company's estimate of annual patient numbers was derived from cancer epidemiology data and an overall risk of VTE in patients with cancer. The potential number of eligible patients rises from 5,127 in year one to 8,319 in year five. Of these patients, the company estimate that 12.8%–13.5% would receive tinzaparin sodium.
- Based on six months duration of treatment and an average weight of 76.5 kg, the company estimate the use of tinzaparin sodium for the extended treatment of VTE in patients with cancer is associated with an estimated budget impact of −£164,633 over five years.
- The cost savings are driven by three main factors: the higher list price of enoxaparin sodium (compared to tinzaparin sodium and dalteparin sodium), the proportion of patients that would receive a dose reduction of dalteparin sodium after one month's treatment and additional clinician time generated by the dose reduction required for dalteparin sodium.
- The Summary of Product Characteristics (SPC) for dalteparin sodium recommends a dose reduction after one month of treatment from 200 units/kg to 150 units/kg body weight. The company have assumed that 48% of patients receive a dose reduction after one month of treatment which would result in an additional GP (50% of cases) or oncologist visit (50% of cases). Shared care arrangements for dalteparin sodium are currently in place in two Health Boards in NHS Wales. Both agreements specify the need for a dose reduction but do not specify the need for an additional consultation to achieve this. Opinion obtained by AWTTC indicates that a dose reduction of dalteparin sodium would not normally generate a GP/consultant visit. The assumption made that only 48% of patients would receive the dalteparin dose reduction was based on a company survey of healthcare professionals in England and Wales.

Additional information:

- The All Wales Medicines Strategy Group (AWMSG) recommends treatment doses of LMWH for VTE in cancer patients are suitable for shared care for up to six months of treatment.

- The National Institute for Health and Care Excellence (NICE) recommends that patients with active cancer and confirmed proximal DVT or pulmonary embolism (PE) are offered a LMWH; treatment should be continued for six months.
- The British Society of Haematology recommends that, in patients with cancer-associated thrombosis, initial treatment should be with a LMWH for six months, if tolerated. Warfarin and other oral anticoagulants are acceptable alternatives if LMWH is impractical and anticoagulation is indicated.
- The company do not anticipate that tinzaparin sodium (innohep® Syringe) will be supplied by a home healthcare provider.

Evidence search:

Date of evidence search: 14 and 15 May 2015
Date of range of evidence search: No data limits were applied to database searches.

Further information:

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Tinzaparin sodium (innohep® Syringe) 20,000 units/ml solution for injection. Reference number: 2369. October 2015.