Scottish Medicines Consortium

fondaparinux, 2.5mg/0.5ml, solution for injection (Arixtra®) No. (287/06)

GlaxoSmithKline

7 July 2006

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

ADVICE: following a full submission

Fondaparinux (Arixtra®) is not recommended for use within NHS Scotland for the prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as those undergoing abdominal cancer surgery.

Fondaparinux showed non-inferiority to one other low molecular weight heparin in preventing VTE in patients undergoing abdominal surgery. The economic case has not been demonstrated.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Fondaparinux, 2.5mg/0.5ml,solution for injection (Arixtra®)

Indication

Prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as those undergoing abdominal cancer surgery.

Dosing information

Fondaparinux sodium 2.5mg/0.5ml, once-daily subcutaneous (SC) injection (pre-filled syringe) given 6 hours following surgical closure provided that haemostasis has been established.

UK launch date

7th July 2005

Cost per treatment course and relevant comparators

Preparation	Dose	Cost (£) up to treatment day 7
Fondaparinux sodium 5mg/ml pre-filled syringe 0.5ml	**2.5mg sc daily from 6h after surgical closure and daily thereafter**	**47**
Dalteparin sodium 2500 units in 0.2ml syringe and dalteparin sodium 5000 units in 0.2ml syringe	2500units 2 hr before induction and 12hr later thereafter 5000 units daily	21
Enoxaparin sodium 40mg (4000units) in 0.4ml syringe	40mg (4000 units) 12 hours before surgery and 24hrly thereafter	29
Tinzaparin sodium 4500 units in 0.45ml syringe	4500units 12 hours before surgery and 24hrly thereafter	25
Reviparin sodium 1432 units in 0.25ml injection	1432units 2hrs before induction and 24hrly thereafter	25
Unfractionated 'low dose' Heparin sodium 5000units/ml.	5000units 2hrs before surgery then 8hrly thereafter	11

NB 1. Only licensed BNFdoses have been chosen as comparator doses.
NB 2. Unfractionated Heparin costs do not include syringes, needles and nursing time for three times daily administration

Summary of evidence on comparative efficacy

Fondaparinux sodium is a synthetic pentasaccharide antithrombotic that selectively binds to antithrombin, which inactivates factor Xa and results in a strong inhibition of thrombin generation and clot formation without affecting thrombin or platelets.

One phase III, randomised, parallel-group, double–blind, double dummy study, compared fondaparinux to the low molecular weight heparin dalteparin in 2927 patients. Patients were

undergoing abdominal surgery expected to last more than 45 minutes under general anaesthesia and either aged over 60 years or over 40 years with at least one additional risk factor for thromboembolic complications. Exclusion criteria included bleeding risk due to a contraindication to dalteparin or fondaparinux.

Patients were randomised to receive once-daily subcutaneous injections of fondaparinux 2.5 mg starting 6 hours after surgical closure or dalteparin 2500 units given 2 hours before induction of anaesthesia and again 12 hours later. Thereafter, dalteparin was given at the once-daily dose of 5000 units. The scheduled duration of treatment was 5-9 days. A mandatory venogram was performed between day 5 and day 10, or earlier in case of symptomatic VTE.

The main efficacy period used for primary and secondary outcome parameters was from the first injection or the day of surgery up to the first venogram or day 10. The whole study period used for symptomatic VTE and also for safety analyses was from the first injection to day 32. The primary outcome was a composite of the following: venogram positive for any deep vein thrombosis (DVT) between day 5 and day 10, symptomatic DVT, non-fatal pulmonary embolism (PE) or fatal PE. The study was originally designed to investigate superiority of fondaparinux for the primary end-point, however, because of a lower than the expected VTE rate, a relative non-inferiority analysis was performed prior to unblinding. The non-inferiority margin was based on an odds ratio with normal approximation for VTE with an upper limit of the 95% CI below 1.70 comparing fondaparinux with dalteparin.

The analysis was conducted on a primary population consisting of 2048 (70%) patients with non-missing VTE assessment. For the primary endpoint, the rate of VTE was 47/1027 (4.6%) with fondaparinux compared with 62/1021 (6.1%) with dalteparin, an absolute risk reduction of 1.5%, p=0.14 and a relative risk reduction of 25% (95% CI –9.0, 47.9, p=0.144). The corresponding odds ratio was 0.74, with an upper 95% confidence limit of 1.09, thus meeting the criteria for non-inferiority of fondaparinux to dalteparin.

A secondary sub-group analysis of the primary endpoint involved cancer surgery patients (69% of the total efficacy population). The rate of VTE was statistically significantly lower with fondaparinux 33/696 (4.7%) than with dalteparin 55/712 (7.7%), p=0.022. This represented an absolute risk reduction of 3.0%, p=0.022 and a relative risk reduction of 39% (95%CI 6.7, 59.6). In those patients who were not undergoing surgery for cancer, the rate of VTE was 14/331 (4.2%) with fondaparinux (95% CI 2.3, 7.0) and 7/309 (2.3%) with dalteparin (95% CI 0.9, 4.6), an observed relative risk reduction with fondaparinux of -86.7 % (95%CI -356.5, 23.6). This result was therefore in favour of dalteparin. For the secondary efficacy endpoints, the rates of symptomatic VTE were similar between treatment groups up to the qualifying assessment and day 32.

Summary of evidence on comparative safety

Analyses were based on an as-treated population (2858 patients) who had received at least one dose of study medication. The primary safety outcome was major bleeding detected in the treatment period between the first injection and two days after the last injection. The incidence was higher with fondaparinux than with dalteparin; 3.4% (95%CI 2.5, 4.5) compared with 2.4% (95% CI 1.7, 3.3), but this was not statistically significant (p=0.122).

Secondary safety outcomes were major bleeds during the whole study period, minor bleeding, transfusion requirements, adverse events/serious adverse events, deaths and changes in laboratory parameters. The rate of major bleeding during the whole study period was higher with fondaparinux 4.3% (95%CI 3.3-5.4) compared with dalteparin 2.7% (95%CI

2.0-3.7), absolute difference 1.5 % (95%CI 0.2-2.9), p=0.032. There was no difference in the proportion of patients experiencing major bleeding, between the fondaparinux 3.4% and dalteparin 2.5% treatment groups for the cancer patient sub group, p=0.355.

There were fewer deaths reported in the fondaparinux group over the whole study period, (2.8% vs 3.9%). The numbers of patients experiencing at least one adverse event, serious adverse event or adverse event leading to study drug discontinuation, were similar between the two treatment groups during the treatment period and the whole study period.

Summary of clinical effectiveness issues

About 30% of the population were excluded from the efficacy analysis because of missing venographic assessment, however the proportion included was similar across the two treatment groups. The sponsors argue that the analysis of the primary efficacy population was reliable on an intention-to-treat basis.

The initial dose of fondaparinux should be given 6 hours following surgical closure provided that haemostasis has been established. The timing of the first fondaparinux injection may have been a contributing factor to the higher rate of bleeding for the fondaparinux group observed in the trial: major bleeding was observed in 9/263 (3.4%) of patients receiving fondaparinux closer to surgery than the protocol dictated compared with 32/1139 (2.8%) of patients who received fondaparinux at least 6 hours after surgical closure. The corresponding figures for VTE were 6.5% and 4.2%. This is not unexpected as higher rates of bleeding are associated with higher levels of VTE prevention.

There is no direct comparison between fondaparinux and low molecular weight heparins (LMWHs) other than dalteparin. Enoxaparin is the most widely used LMWH in the UK but has not been compared directly with either fondaparinux or dalteparin. SIGN 62 (2002) states that LMWHs vary in their manufacture, chemistry and biology, but it is not clear whether or not these characteristics affect clinical efficacy or safety equivalence. ACCP (American College of Chest Physicians) guidelines published in 2001 state that few studies have directly compared two LMWHs and that to date the limited available data suggest that any observed differences between LMWHs are similar to the variability between different trials using the same LMWH.

Summary of comparative health economic evidence

A cost-effectiveness/utility analysis was performed for fondaparinux versus enoxaparin, a LWMH, in patients with cancer undergoing abdominal surgery. This used a sub-set of data for cancer patients from a phase III clinical trial comparing fondaparinux with dalteparin for patients undergoing abdominal surgery (PEGASUS study). For this sub-group enoxaparin was used as the comparator in the economic evaluation as it is more frequently used in the UK than dalteparin. As there are no comparative data for fondaparinux versus enoxaparin, data for dalteparin for the cancer surgery sub-group from PEGASUS was used as a proxy for the outcomes expected with enoxaparin. The manufacturer based this assumption of equivalent outcomes on evidence within SIGN and American College of Chest Physicians guidelines, and a review conducted by the manufacturer of clinical studies of each drug versus a common comparator (unfractionated heparin). The review was not systematic and hence provides only partial support for the equivalence of outcomes assumption.

As the main clinical trial (PEGASUS) only had a very short follow-up of 1 month with data available on incidence of asymptomatic DVTs, epidemiological modelling was used to

estimate disease progression to symptomatic VTEs. A risk equation approach was used with parameters for asymptomatic DVT to symptomatic VTE risk derived from studies in orthopaedic surgery. The base case estimate was that 19.6% of patients with an asymptomatic DVT initially would develop a symptomatic VTE, which carries an elevated risk of mortality by day 90. Published mortality risk data for patients (not cancer specific) with symptomatic VTEs, adapted to reflect the greater mortality risk for the cancer surgery patients in the economic model, was used in order to obtain 15 year survival estimates for patients on fondaparinux and enoxaparin. The main results were a net cost difference of £20.33 per patient with an estimated survival gain of 20 days per patient receiving fondaparinux compared to enoxaparin producing an incremental cost per life year gained and QALY gained of £371 and £447 respectively. The QALY calculation is based on an estimated utility of 0.83 for patients undergoing colorectal cancer surgery. However, the quality of life impact due to fondaparinux patients experiencing fewer VTE's was not determined.

The economic evaluation was constrained by the short follow-up and the lack of data on symptomatic VTE's in the clinical trial, thereby requiring extensive epidemiological modelling in order to evaluate cost-effectiveness. In addition, the estimate of survival benefit depended on the difference in the within trial mortality between fondaparinux and the comparator, which was not statistically significant and included deaths unrelated to VTE. The magnitude of the survival benefit for fondaparinux use is therefore uncertain and cost-effectiveness has not been demonstrated.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated a budget impact of fondaparinux used in the high-risk group of patients undergoing abdominal cancer surgery of £13,000 in 2006, up to £66,000 in 2011. If savings associated from a reduced use of enoxaparin are taken into account the net budget impact is estimated at £5,000 in 2007 rising to £24,000 in 2011.

Guidelines and protocols

The SIGN (Scottish Intercollegiate Guidelines Network) guidelines on the Prophylaxis of Venous Thromboembolism- A National Clinical Guideline. 62, 1-51, published October 2002. A review of this guideline is due to be published in 2008.

The NICE (National Institute for Clinical Excellence) guidelines on Venous Thromboembolism: the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients undergoing orthopaedic surgery and other high-risk surgical procedures, is due to be published in 2007.

The ACCP (American College of Chest Physicians), Guidelines on the Prevention of Venous Thromboembolism, published in 2001 in CHEST.

Additional information

The Scottish Medicines Consortium (SMC) accepted fondaparinux for use in NHS Scotland in November 2002 for prevention of venous thrombo-embolic events in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery.

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.

This assessment is based on data submitted by the applicant company up to and including ***16 June 2006.***

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

The undernoted references were supplied with the submission.

Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. PEGASUS. Br J Surg. 2005;92:1212-20.

Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FAJ et al. Prevention of venous thromboembolism. Chest. 2001;119:132S-75S.