

National PBM Drug Monograph Addendum Fondaparinux (Arixtra®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Please see the original drug monograph at:

<http://vaww.pbm.med.va.gov/drugmonograph/fondaparinuxreview.pdf>

Introduction

Since the approval of fondaparinux in December 2001 and the subsequent monograph review in 2002, several clinical trials have investigated the use of fondaparinux in other thrombotic conditions such as pulmonary embolism, symptomatic deep vein thrombosis and orthopedic procedures. Additionally Phase II and III trials are investigating its use in acute coronary syndrome, ST elevation MI and venous thromboembolism. Trials investigating the duration of thromboembolism prophylaxis with fondaparinux as well as economic variables have been conducted.

These trials may hold findings that could impact the formulary status of the agent or suggest that criteria for use be developed for the agent.

Pulmonary Embolism

The standard of care for acute pulmonary embolism (PE) has involved hospitalization and initiation of systemic anticoagulation with unfractionated heparin (UFH). This therapy requires frequent laboratory monitoring and dose adjustments. Fondaparinux offers the advantage of once daily injection and no laboratory monitoring. The Matisse Investigators¹ undertook an open label trial of fondaparinux versus standard therapy in 2213 patients with acute, symptomatic PE. The dose of fondaparinux was weight adjusted, 5.0 mg, 7.5 mg, 10 mg for body weights of <50 kg, 50-100 kg and >100 kg, respectively. UFH therapy maintained an activated partial thromboplastin time of 1.5-2.5 times control. The primary efficacy outcome was symptomatic recurrent venous thromboembolism during the three-month study period. This was defined as occurring if patients developed objective evidence of recurrent PE or deep vein thrombosis or if death from PE could not be ruled out. For the primary outcome, fondaparinux demonstrated recurrence in 3.8%, UFH in 5.0% (absolute risk reduction -1.2, 95% CI -3 to 0.5). This translates to a NNT of 83. In terms of adverse effects, the incidence of major bleeding during initial treatment in the fondaparinux group was 1.3%, UFH 1.1% (absolute risk reduction 0.2%, 95%CI -0.7 to 1.1). This translates to an NNH of 5.

This trial demonstrated that fondaparinux and enoxaparin have a similar safety and efficacy profile in the treatment of PE.

In June 2004, fondaparinux received FDA approval for the treatment of PE.

Symptomatic Deep Venous Thrombosis

In June 2004, the results of the fondaparinux versus enoxaparin in the initial treatment of symptomatic VTE conducted by the Matisse Investigators were published². This trial was conducted worldwide and involved 2205 patients with acute, symptomatic VTE. The dose of fondaparinux was weight adjusted, 5.0 mg, 7.5 mg, 10 mg for body weights of <50 kg, 50-100 kg and >100 kg, respectively. Enoxaparin was dosed at 1 mg/kg twice daily. Both agents were given for at least 5 days and until vitamin K antagonists achieved an international normalized ratio greater than 2.0. The primary study outcome was the 3-month incidence of symptomatic, recurrent VTE. The development of the primary outcome occurred in 3.9% of fondaparinux treated patients versus 4.1% of enoxaparin treated patients (95% CI -1.8 to 1.5, NNT=5). There was no significant difference in the development of major bleeding between the two groups (fondaparinux 1.1%, enoxaparin 1.2%).

In June 2004, fondaparinux received FDA approval for the treatment of VTE.

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Prophylaxis in Major Orthopedic Surgery

The pivotal trials for approval of fondaparinux involved patients undergoing knee replacement surgery and hip fracture surgery (PENTAMAKS³ and PENTHIFRA⁴, respectively). Subsequently, two trials have investigated the use of fondaparinux in elective hip surgery (EPHESUS⁵) and in total hip replacement (PENTATHLON 2000⁶). The EPHESUS trial was conducted in Europe and utilized an enoxaparin dose of 40 mg daily. The primary efficacy outcome for this trial was venous thromboembolism (deep vein thrombosis, pulmonary embolism or both) measured at day 11. The absolute risk reduction was 5% (95% CI 8.1%-2.7%, p<0.0001) for fondaparinux versus enoxaparin correlating to an NNT of 20. The number of neither patients with major bleeding nor those with a bleeding index >2 were different between the two treatment groups (<1% in both groups and 4% versus 3% for fondaparinux, enoxaparin respectively). The PENTATHALON 2000 trial was the North American counterpart of the previous trial. This trial used fondaparinux at the same dose as in EPHESUS (2.5 mg daily) but enoxaparin was dosed at 30 mg twice daily. The absolute risk reduction in this trial was 2% (95% CI 5.5% to 0.6%, p=0.099) and NNT 50. Safety outcomes of this trial were the same as the previous trial, the two groups did not differ significantly in terms of major bleeding or patients with a bleeding index of >2.

Turpie, et al, conducted a meta-analysis⁶ of these four orthopedic prophylaxis trials.⁷ They found no difference between the groups in terms of age, weight, previous venous thromboembolism and previous orthopedic surgery. There were 3616 patients in the fondaparinux group and 3621 in the enoxaparin group. It should be remembered that differing doses of enoxaparin were used in these trials dependent on location of the trial (Europe versus North America). The fondaparinux treated group developed venous thromboembolism by day 11 in 182 of 2682 patients and the enoxaparin group in 371 of 2703 patients. This results in a common odds reduction of 55.2% (95% CI 45.8% to 63.1%, p<0.001). The incidence of clinically significant bleeding did not differ between the groups.

These trials demonstrate fondaparinux to have greater efficacy than enoxaparin in regards to VTE prophylaxis after major orthopedic surgery. Currently, low molecular weight heparin (LMWH) has a Grade 1A recommendation from the American College of Chest Physicians (2001) for elective hip and knee replacement. The use of LMWH in hip fracture has a grade 1B recommendation. Since fondaparinux has shown greater efficacy with equivalent safety to enoxaparin in PENTHIFRA, it may be deemed a reasonable alternative in hip fracture prophylaxis. The update of the ACCP recommendations is due to be released in the summer of 2004.

Duration of Prophylaxis

Eriksson, et.al.⁸ demonstrated the benefit of fondaparinux versus placebo for 1 month after hip fracture surgery. In this trial patients received fondaparinux 2.5 mg daily for 6-8 days after surgery and were then randomized to receive placebo or continue with their current regimen. The primary outcome was venous thromboembolism (deep vein thrombosis, pulmonary embolism or both) measured at day 25 to 32. The absolute risk reduction for fondaparinux versus placebo was 33.6% (95% CI 41.4% to 26.5%, p<0.001). This correlates to an NNT of 3. The utility of extended prophylaxis with LMWH has been defined in earlier trials^{9,10}.

Cost Effectiveness Evaluations

Incremental cost analysis based on clinical trial results has been conducted with fondaparinux. These studies have been conducted on the major clinical trials of Fondaparinux in orthopedic indications. The economic trials have been conducted from a healthcare payer standpoint and involved only direct costs. A cost effectiveness study based on the Bauer, et al trial compared fondaparinux to enoxaparin.¹¹ This trial involved VTE prophylaxis in knee surgery and compared fondaparinux 2.5 mg daily for 5 days to enoxaparin 30 mg twice daily for 4 days. The analysis showed a \$1081.33 cost savings for fondaparinux per VTE avoided. In contrast, a cost effectiveness analysis of the Eriksson, et al. trial for VTE prophylaxis in hip fracture demonstrates that costs of \$573.20 would be incurred if fondaparinux were utilized in place of enoxaparin.¹² Both of the cost effectiveness trials were conducted post hoc, employed adverse event rate, doses and outcomes from the pivotal trials and came to conflicting conclusions.

Sullivan, et al.¹³ have conducted a cohort simulation model of a 7 day prophylactic regimen with either fondaparinux or enoxaparin which subsequently followed patients for 30 days, 90 days and 5 years post discharge. The use of fondaparinux was associated with a cost saving of \$2, \$76, \$100 at discharge, 1 month, and 3 months respectively. This was seen across all treatment types but most robust with the use in hip fracture surgery.

The trials from Turpie, et al. and Lassen, et al. were the basis for a cost effectiveness analysis¹⁴ which demonstrated that fondaparinux could produce savings of \$ 6612.11 per VTE avoided in comparison to enoxaparin 40 mg once daily. However, the use of enoxaparin 30 mg twice daily demonstrated a cost savings of \$50,171.89 per VTE avoided. This analysis was limited to proximal VTE and non fatal PE. The design did factor in the associated bleeding rates from the studies.

Ongoing trials

Several trials are currently underway regarding the use of fondaparinux for conditions such as medical indications (ARTEMIS), acute coronary syndrome and VTE prophylaxis in abdominal surgery (PEGASUS fondaparinux versus dalteparin). These trials will help to answer remaining questions regarding the place in therapy for this agent.

Conclusion

Fondaparinux administered 6-8 hours after surgery has demonstrated greater or equivalent efficacy to enoxaparin in VTE prophylaxis for major orthopedic procedures. The use of fondaparinux in the treatment of symptomatic VTE has demonstrated equivalent safety and efficacy to twice daily enoxaparin. The use of fondaparinux has demonstrated equivalent efficacy to UFH in the treatment of PE. Additionally, the safety profile is equivalent with no increase in major or minor bleeding over the LMWH preparation. There have been several cost effectiveness analysis based on the outcomes of these clinical trials. The results of these trials do not consistently demonstrate fondaparinux to be more cost effective. They have displayed a possible association with enoxaparin dose used as comparator as well as surgery type. Further analysis is required to demonstrate a consistent outcome.

Current Prices

Drug	Dose	FSS price	Cost per day
Dalteparin	2500 units	\$7.64*	\$7.64*
Dalteparin	5000 units	\$12.37*	\$12.37*
Enoxaparin	30 mg	\$8.90	\$17.80
Enoxaparin	40 mg	\$12.08	\$12.08
Fondaparinux	2.5 mg	\$18.09	\$18.09

*BIG4 pricing not FSS

These prices are current as of 5/3/04. To determine current prices after this date please refer to our web site at www.pbm.med.va.gov

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