**South African National Essential Medicines List**
**Adult Hospital Medication Review Process**
COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSES
Fondaparinux for the **treatment of venous thromboembolism** in hospitalised patients in the South African public health system.

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*Conflict of Interest:* None declared.

# 1. INTRODUCTION

***Medication:*** Fondaparinux sodium (fondaparinux), 2.5mg/0.5mL; 5mg/0.4mL; 7.5mg/0.6mL; 10mg/0.8mL

***Background:***
A motivation was submitted by the Western Cape Provincial Pharmaceutics and Therapeutics Committee to consider fondaparinux sodium as an alternative to either unfractionated heparins (UFH) and low molecular weight heparins (LMWH) to the Adult Hospital Expert Review Committee (AH-ERC) of the National Essential Medicines List Committee[1]. The indications included treatment of Acute Coronary Syndromes (ACS), prophylaxis for venous thrombosis treatment of venous thromboembolism in adults. Thus, technical support was requested from Supply Chain Technical Assistance (SCTA), USAID for a costing analysis on fondaparinux sodium (including cost-effectiveness, budget impact analyses and international price comparison analyses) compared to LMWH, enoxaparin and UFH, currently recommended in the Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicine List (EML)[2].

This cost-effectiveness analysis attempts to make reasonable estimations of the health system budget impact and cost-effectiveness of the use of fondaparinux in the treatment of venous thromboembolism (VTE) compared to enoxaparin in the South African public health system. While current formulations of UFH available in South Africa could potentially be used for treatment of VTE no alternative agents available, it was not considered that UFH represents an appropriate comparator in this indication for this analysis. The report is developed for consideration by the Adult Hospital Evidence Review Committee (AH-ERC) and the National Essential Medicines List Committee (NEMLC), and is intended to aid consideration of the listing of

[1] Minutes of the Adult Hospital Level meetings, 26 October 2017 and 23 November 2017.
[2] Adult Hospital Level STGs and EML, 2015.

fondaparinux on in the Adult Hospital Standard Treatment Guideline (AHSTG) and the National Essential Medicines List (EML).

Based on current procurement volumes, it is estimated that approximately 3,000 patients annually currently receive treatment for VTE with existing anticoagulants (enoxaparin or unfractionated heparin) in the public health system at an existing national medicine procurement and administration cost of R1.1 million annually[3]. As information about underlying prevalence of clinically significant VTE (from deep vein thrombosis (DVT) to pulmonary embolism (PE)) in South Africa is unknown, it is uncertain what proportion of the patient population in need of VTE treatment is currently achieving access. Epidemiological data in the US indicates that first-time VTE incidence occurs in approximately 0.1% of the population, with increasing incidence associated with advanced age and co-morbidities[4]. A 0.1% incidence in South Africa would indicate a potential patient population between 30,000 - 40,000 people (adjusted for public sector utilisation) in need of VTE treatment. US data indicates that mortality associated with VTE is approximately 6% in cases of DVT, and 12% of cases in PE[5].

Concurrent to this assessment, the use of fondaparinux is also being considered in the prophylaxis of VTE, ST-Elevation Myocardial Infarction (STEMI), and Non-ST Elevation Myocardial Infarction (NSTEMI). Although these concurrent analyses also consider the use of fondaparinux, they involve different patient populations, underlying clinical evidence, dosing regimens, and have differing cost and cost-effectiveness outcomes. The recommendations following the different analyses should therefore be considered independent to one another.

## 2. INDICATIONS

Fondaparinux is an anticoagulant medication registered by the Medicine Control Council (MCC) and is currently licenced for use in South Africa in the management of ACS and the prophylaxis of VTE. Fondaparinux is not currently licenced in South Africa for the treatment of VTE. The MCC-licenced indications for enoxaparin related to VTE treatment are listed in table 1.

| UFH | Enoxaparin | Fondaparinux |
|---|---|---|
| Treatment of arterial and venous thrombosis[6]. | Treatment of deep venous thrombosis with or without pulmonary embolism[7] (safety of home treatment for this indication has not been established.) | Not indicated[8] |

**Table 1 MCC licenced indications for enoxaparin, UFH heparin and fondaparinux in treatment of VTE (as of February 2018, text extracted from Patient Information Leaflets)**

Fondaparinux is being considered in the VTE-treatment indications as listed in the existing Adult Hospital Standard Treatment Guideline (2015) as detailed in Table 2. The existing treatments recommended in the indications below are enoxaparin or UFH. The Adult Hospital Level Committee considered the evidence submitted for fondaparinux for VTE-treatment, as described in section 4: Clinical Inputs.

[3] 3,000 patients based on procurement volumes Contract Circular HP06-2017SVP. See table 11 for treatment costs
[4] White, R.H., 2003. The epidemiology of venous thromboembolism. *Circulation*, *107*(23 suppl 1), pp.I-4.
[5] Ibid.
[6] South African package insert and patient information leaflet for heparin sodium: BODENE PTY (LTD) Heparin sodium-fresenius http://home.intekom.com/pharm/intramed/heparin.html
[7] South African package insert and patient information leaflet for enoxaparin sodium: Sanofi-Aventis Clexane (hard copy)
[8] South African package insert and patient information leaflet for fondaparinux sodium: Pharmacare Limited Arixtra (hard copy)

| Chapter of AH STG | Disorder | Indication |
|---|---|---|
| 2. Blood and Blood Forming Organs | 2.14 Venous Thromboembolism | Treatment of proximal venous thrombosis and/or pulmonary embolism |

**Table 2. Listed indications for enoxaparin: South African National Standard Treatment Guidelines (Adult Hospital Level STGs and EML, 2015)**

# 3. METHODS

The approach to the assessment is informed by the methodological principles detailed in the International Decision Support Initiative Reference Case[9] and the South African Guidelines for Pharmacoeconomic Analysis[10]. The methodological approach is also informed by previous approaches to costing analysis to support EDP Medicine Reviews and discussion with EDP team (T Leong) and ERC Lead Reviewers (Prof P Commerford and Dr R Griesel).

The assessment involved a cost effectiveness analysis (CEA) and a budget impact analysis (BIA) compared to existing treatments as detailed in Table 3 below.

| Indication | Population | Intervention | Comparator | Outcomes | Perspective |
|---|---|---|---|---|---|
| Treatment of VTE | Adult patients admitted for management of VTE | fondaparinux | *Base case:* enoxaparin | • VTE recurrence<br>• Major bleed<br>• Death<br>• QALYs<br>• Total cost to health system (annual and 5-year NPV)<br>• Recommended national tender price for fondaparinux | South African national public health system |

**Table 3. Summary table of approach to analyses**

A decision analytic model was developed that estimated the likely clinical outcomes and costs associated with using fondaparinux compared to enoxaparin in the treatment of VTE (figure 1). Effects and costs were estimated for the immediate treatment period, and extrapolated over a lifetime time horizon. The model consists of a decision tree for the initial inpatient stay where either fondaparinux or enoxaparin is administered. During admission, patients are at risk of a major bleed or HIT (heparin-induced thrombocytopenia) and/or a VTE recurrence. To capture progression following discharge, a Markov-model structure was developed where each year, patients will move into either a state of "Survive" (otherwise well post an admission for VTE), "Survive with HIT complications", or "Die". The probability of a patient initially entering into any of the long-term Markov states (including death) is dependent upon outcomes in the initial treatment period. The Markov model is then run for 50 years, using an annual discount rate of 3% for costs and effects. At the end of the final cycle, all patients will have assumed to have died as a result of natural expected mortality rate across the population, or as a result of complications from VTE, HIT or major bleed.

[9] Wilkinson T, Sculpher MJ, Claxton K, Revill P, Briggs A, Cairns JA, Teerawattananon Y, Asfaw E, Lopert R, Culyer AJ, Walker DG. The international decision support initiative reference case for economic evaluation: an aid to thought. Value in Health. 2016 Dec 1;19(8):921-8..
[10] Guidelines for Pharmacoeconomic Analysis 2012. National Department of Health, South Africa (the guidelines apply to analysis conducted to inform pharmaceutical pricing regulations in the South African private sector (the Single Exit Price), and so are partially applicable for public sector decision making.

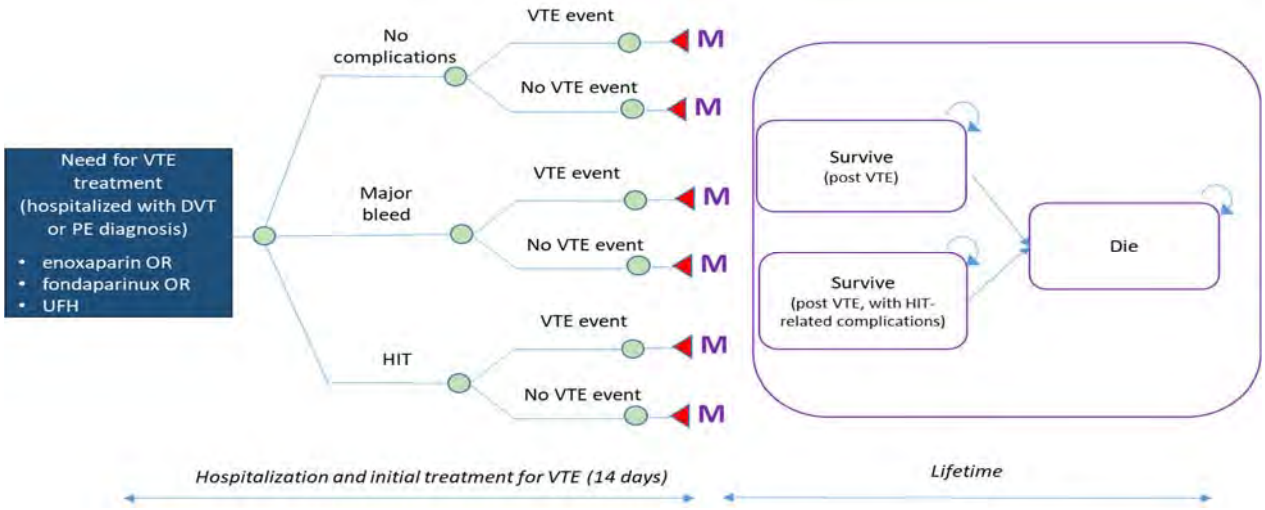


**Figure 1. Decision analytic model structure to estimate cost effectiveness of fondaparinux in VTE treatment** *(UFH subsequently removed as a comparator and not included in analysis presenting in this report)*

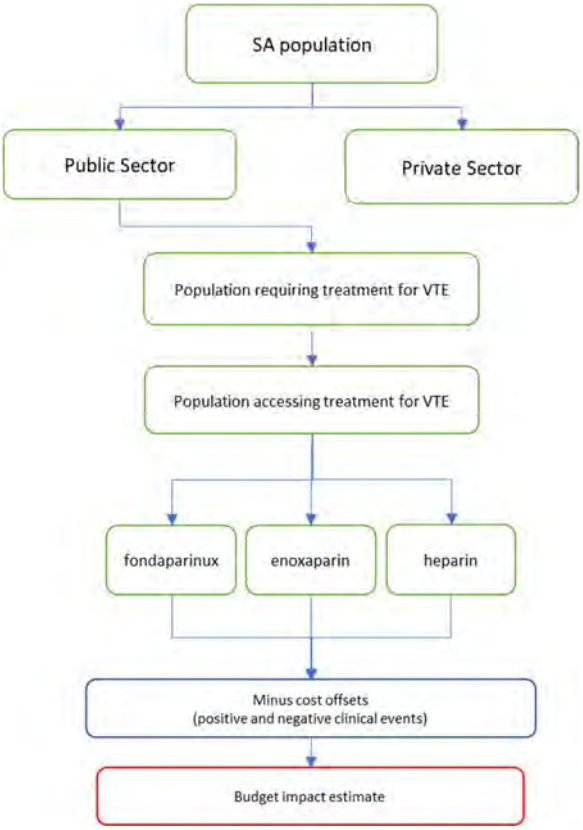


**Figure 2. Framework to estimate budget impact of introducing fondaparinux to the South African health system in VTE treatment** *(UFH subsequently removed as a comparator and not included in analysis presenting in this report*

A budget impact analysis was developed to explore the likely costs to the South African public health system of introducing fondaparinux as a treatment option for the treatment of VTE as an alternative to enoxaparin. The budget impact estimate is based on the annual cost if the entire existing patient population who accesses VTE treatment was switched to fondaparinux. In reality, local prescribing and market supply would result in a proportion of the market switching from enoxaparin to fondaparinux, however the presentation of an extreme scenario is likely to provide some indication of the expected upper limit of the budget impact at a national level. In addition, the budget impact represents only those

patients who would access the public health system, and is adjusted by those who are likely to access treatment, as informed by existing volumes of enoxaparin treatment -doses procured under national tender. Cost offsets such as reduced need for management of complications and cases of VTE is then added to the budget impact to represent the final result, with key assumptions tested in sensitivity analysis.

## 4. Clinical Inputs

Clinical effects were derived from the motivation submitted by the Western Cape Provincial Pharmacy and Therapeutics Committee (Appendix I). The key trial are detailed in Table 4.

Where clinical inputs were unavailable or not applicable, expert opinion from ERC committee members, Prof P Commerford and Dr R Griesel, was used (Refer to Appendix IV for declared conflicts of interests).

| First author, publication year | Study type | Main Study Findings |
|---|---|---|
| **Buller *et al*. 2003** | RCT | The RCT compared fondaparinux and unfractionated heparin (UFH) for the treatment of symptomatic PE. The main efficacy outcome evaluated was recurrence of VTE and the main safety outcome was major bleeding. Incidence of VTE recurrence was 3.8% and 5% in the fondaparinux and UHF treatment groups respectively. Major bleeding occurrence was higher in the fondaparinux group (1.3%) than UFH group (1.1%). |
| **Buller *et al*. 2004** | RCT | The RCT compared fondaparinux and enoxaparin for the treatment of DVT. The main efficacy outcome evaluated was recurrence of VTE and the main safety outcome was major bleeding. Incidence of VTE recurrence was 3.9% and 4.1% in the fondaparinux and enoxaparin treatment groups respectively. Major bleeding occurrence was higher in the enoxaparin group (1.2%) than fondaparinux group (1.1%). |
| **Gordois *et al*. 2003** | Economic Evaluation | Cost-effectiveness of fondaparinux compared to enoxaparin for thromboembolism prophylaxis Parameters for death from major bleed and pulmonary embolism calculated through meta-analysis (0.0063 and 0.1398) respectively. |
| **Robertson *et al*. 2017** | Cochrane review | Comparison of low molecular weight heparins (LMWH) and UFH for treatment of venous thromboembolism. Safety outcome for HIT evaluated with probability of 0.0005 for enoxaparin. |
| **Zinkovsky *et al.* 2008** | Peer reviewed article | Review of Heparin-Induced Thrombocytopenia (HIT). Probability of dying from HIT stated as 0.15. |

**Table 4. Pivotal trials and reviews – treatment of VTE**

The main clinical effects for consideration in the assessment are detailed in Table 5 and include any differences in the risk associated with receiving treatment with either fondaparinux or enoxaparin relating to development of HIT, recurrence of a VTE, suffering a major bleed, and death.

| Description | Value | Lower value | Upper value | Source |
|---|---|---|---|---|
| Probability of VTE fondaparinux | 0.039 | 0.029 | 0.049 | Buller et al. 2004 |
| Probability of VTE enoxaparin | 0.041 | 0.031 | 0.051 | Buller et al. 2004 |
| Probability of HIT fondaparinux | 0 | 0 | 0 | [11] |
| Probability of HIT enoxaparin | 0.0005 | 0.000375 | 0.000625 | Robertson *et al.* 2017 |
| Probability of Major Bleed fondaparinux | 0.011 | 0.00825 | 0.01375 | Buller *et al*. 2004 |
| Probability of Major Bleed enoxaparin | 0.012 | 0.009 | 0.015 | Buller *et al*. 2004 |
| Probability Death with PE | 0.1398 | 0.10485 | 0.17475 | Gordois *et al.* 2003 |
| Probability Death with Major Bleed | 0.0063 | 0.004725 | 0.007875 | Gordois *et al.* 2003 |
| Probability Death with HIT | 0.15 | 0.1125 | 0.1875 | Zinkovsky *et al.* 2008 |

**Table 5. Key clinical inputs**

## Utilities

The long-term impact of outcomes associated with treatment for VTE are calculated by applying an annual estimate of the health-related quality of life that is associated with being in a particular state of either surviving without complications, surviving with VTE related complications, Surviving with HIT related complications or death (table 6). The annual costs incurred in a particular state are detailed in table 10, with death incurring no annual recurring cost or utility.

| Parameter | Value | Lower value | Upper value |
|---|---|---|---|
| Survival Without Complications | 0.96 | 0.75 | 1 |
| Survival With VTE related Complications | 0.7 | 0.525 | 0.875 |
| Survival With HIT related Complications (only enoxaparin-related) | 0.5 | 0.375 | 0.625 |
| Death | 0 | 0 | 0 |

**Table 6. Markov state utilities**

## State transition probabilities

The state transition probabilities are calculated from clinical inputs listed in table 5 and determine the chance that a patient will move from one state to another over time. The probabilities are shown in table 7 (initial transitions from the hospitalisation to the long-term states) and table 8 (recurring transitions between the long-term states). For example, the probability that a patient will move from “Survival without Complications” to “dead” in any one year is 0.03, and includes the underlying average mortality rate in South Africa for that age group. Patients moving to the “Survial with VTE complications” and Survival with HIT complications” will be at a 0.1398 and 0.15 one-off risk of death respectively in the base year, with the recurring rate of death the same across disease states over time. In this analysis, it is assumed that patients would not move between “Survival with VTE Complications” and “Survival with HIT Complications” as HIT would have occurred at the point of hospitalisation.

[11] Fondaparinux is not a heparin derived product

Markov state transition probabilities

| | Survival without complications | Survival with VTE Complications | Survival with HIT complications | Dead |
|---|---|---|---|---|
| Survival without complications | 0.97 | 0 | 0 | 0.03 |
| Survival with VTE complications | 0 | 0.97 | 0 | 0.03 |
| Survival with HIT complications | 0 | 0 | 0.97 | 0.03 |
| Dead | 0 | 0 | 0 | 1 |

**Table 8. Transition probabilities between long-term Markov states (stage 1)**

The central assumptions for the model are that

- Patient enters Markov transition model after completion of treatment
- Each transition state has a one year cycle length
- A patient does not experience any long-term complications because of a major bleed – the negative health effects of the major bleed are experienced immediately during hospital stay and the patient will either recover or die at that point.

# 5. Cost Inputs

The main cost effects included in the assessment were associated with procurement costs of the different anticoagulants and hospital costs associated with management of VTE, HIT, and major bleed. The central costing parameters were drawn from the Pharmaceutical tenders for the State sector, the Uniform patient fee schedule (2017), national staff payment schedules, and previous NEMLC approved costing analyses[12].

Fondaparinux is not currently on the EML thus there is no comparative contract price however utilising the comparison from the table below, an estimate of 20% was applied to determine the potential estimated price (refer to the international pricing analysis report for details).

| Enoxaparin | Formulation | Contract Price (South Africa) | SEP (South Africa) | International Average |
|---|---|---|---|---|
| Prophylaxis | 40mg/0.4mL | R 27.70 | R 206.41 | R 41.97 |
| Treatment | 60mg/0.6mL | R 84.40 | R 394.08 | R 120.06 |
| | 80mg/0.8mL | R 88.66 | R 352.98 | R 149.31 |
| | 100mg/1mL | NA | R 317.74 | R 171.21 |

**Table 9: Comparison of contract price, single exit price and international average ex-manufacturer's price for enoxaparin formulations (average daily cost)**

[12] Rivaroxaban for stroke prevention in atrial fibrillation – Pharmacoeconomics and budget impact analysis 2015 (Appendix II)

| Fondaparinux | Formulation | Estimated Price | SEP (South Africa) | International average |
|---|---|---|---|---|
| Prophylaxis | 2.5mg/0.5mL | R 41.59 | R 207.91 | R 158.06 |
| Treatment | 5mg/0.4mL | R 63.34 | R 316.70 | R 194.05 |
| | 7.5mg/0.6mL | R 63.34 | R 316.70 | R 319.10 |
| | 10mg/0.8mL | R 63.34 | R 316.70 | R 576.29 |

**Table 10: Comparison of estimate contract price, single exit price and international average ex-manufacturer's price for fondaparinux formulations (average daily cost)**

| Medicine | Dosage | Formulation | Unit cost | No. of units daily | Medicine cost (per day) | Administration Cost (per day) | Treatment duration (days) | Total Cost for treatment |
|---|---|---|---|---|---|---|---|---|
| **fondaparinux** | SC, 7.5mg daily | 7.5mg | R63.34 | 1 | R63.34 | R4.12 | 14 | R944.45 |
| **enoxaparin** | SC, 1 mg/kg 12 hourly | 80mg | R44.33 | 2 | R88.66 | R17.05 | 14 | R1,317.96 |

**Table 11. Total regimen costs with 70kg used to calculate weight-based average treatment doses**

The total administration costs for the different treatment regimens were constructed from the unit cost of the medicine, multiplied by the expected number of doses required and any applicable administration costs which were calculated on the assumption that each patient stay where the different agents were administered would require and initial three minutes doctor time to assess and prescribe, and a dispensing fee. Each administration was estimated to require two minutes of nurse time for fondaparinux and enoxaparin. The daily administration cost is then multiplied by the number of days treatment and added to the medicine cost for the total number of days treatment to determine the "Total Cost for treatment" in Table 12 below. The calculations for the cost workup in table 10 and 11 are available in attached Excel workbook.

| Description | Value | Lower value | Upper value | Source |
|---|---|---|---|---|
| ***Once-off Costs (Decision Tree)*** | | | | |
| Cost for treatment of enoxaparin per patient | R1,317.96 | R 988.47 | R 1 647.45 | Contract Circular[13] HP06-2017SVP |
| Cost for treatment of fondaparinux per patient | R944.45 | R 708,34 | R 1 180,57 | See Tables 9 -11 |
| Cost of treating a major bleed | R 11 268 | R8 451 | R14 085 | UPFS 2017[14] |
| Cost of treating HIT | R19,646 | R14 735 | R24 558 | UPFS 2017 |
| Cost of treating a VTE event | R 21 383 | R16 037 | R26 729 | UPFS 2017 |
| Costs associated with a patient dying | R 368 | R276 | R460 | UPFS 2017[15] |
| ***Recurring costs (annual)*** | | | | |
| Costs of patient without complications | R500 | 375 | 625 | UPFS 2017 |
| Costs of patient with VTE related complications | R17 000 | 12750 | 21250 | UPFS 2017 |
| Costs of a patient with HIT related complications | R17 000 | 12750 | 21250 | UPFS 2017 |

**Table 9. Model cost inputs**

[13] http://www.health.gov.za/index.php/medicine?download=2649:master-procurement-catalogue-05-february-2018
[14] South African Uniform Patient Fee Schedule. National Department of Health 2017
[15] Cost of dying as listed in the UPFS and reflects death certificate and mortuary costs

# 6. Results

## a. Cost effectiveness analysis

Listing fondaparinux for prophylaxis of VTE is estimated to avoid 9 cases of major bleed, 14 cases of HIT, and 2 deaths compared to enoxaparin in the 3,000 patients estimated to be treated annually for VTE in South Africa. The resultant Incremental Cost Effectiveness Ratios (ICERs) are in Table 11 and displayed in figure 3. Fondaparinux generates more QALYs at an overall net reduced cost compared to enoxaparin. The price of fondaparinux used in the analysis is 20% of the current SEP.

| Strategy | Cost | Incr Cost | Eff | Incr Eff | Incr C/E |
|---|---|---|---|---|---|
| Fondaparinux | R14,970 | | 23,77 | | |
| Enoxaparin | R15,537 | R567 | 23,76 | -0,01 | Dominated |

**Table 11. Summary of cost effectiveness of fondaparinux in the treatment of VTE**

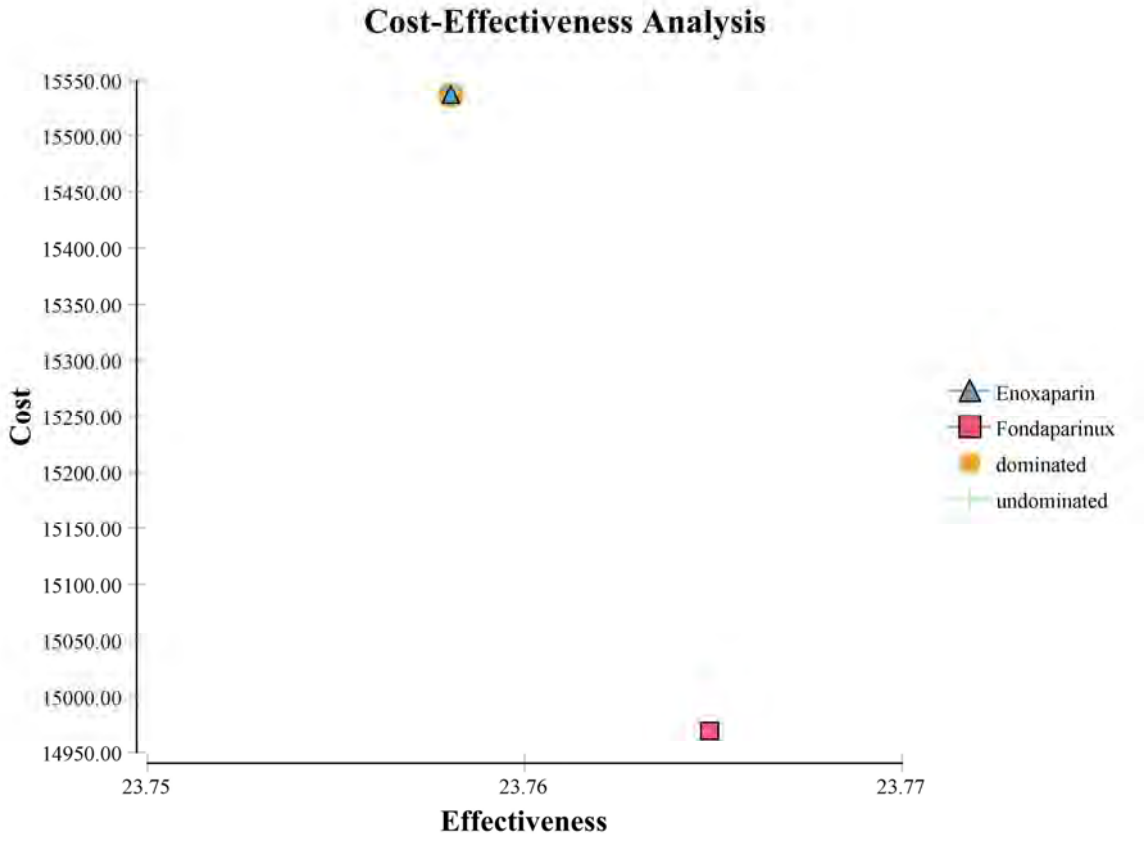


**Figure 3: Cost-effectiveness plane VTE treatment**

**Sensitivity analysis**

One-way sensitivity analysis was conducted on the major clinical and cost parameters to generate the Tornado diagram in figure 4 (fondaparinux vs enoxaparin). Each bar on the diagram represents the change in the ICER that is associated with changes in the input parameter, with inputs ranked by the

magnitude of the change. The diagram below shows that the cost of enoxaparin fondaparinux had an impact on the results but not substantial enough to change the interpretation.

A limitation of one-way sensitivity analysis is that parameters rarely move independently of one another (e.g. if the cost of managing a major bleed increases, the cost of managing a VTE is also likely to increase). More complex sensitivity analysis, (e.g. probabilistic sensitivity analysis) is beyond the scope of this assessment. However, this basic sensitivity analysis provides a general overview for key drivers of uncertainty.

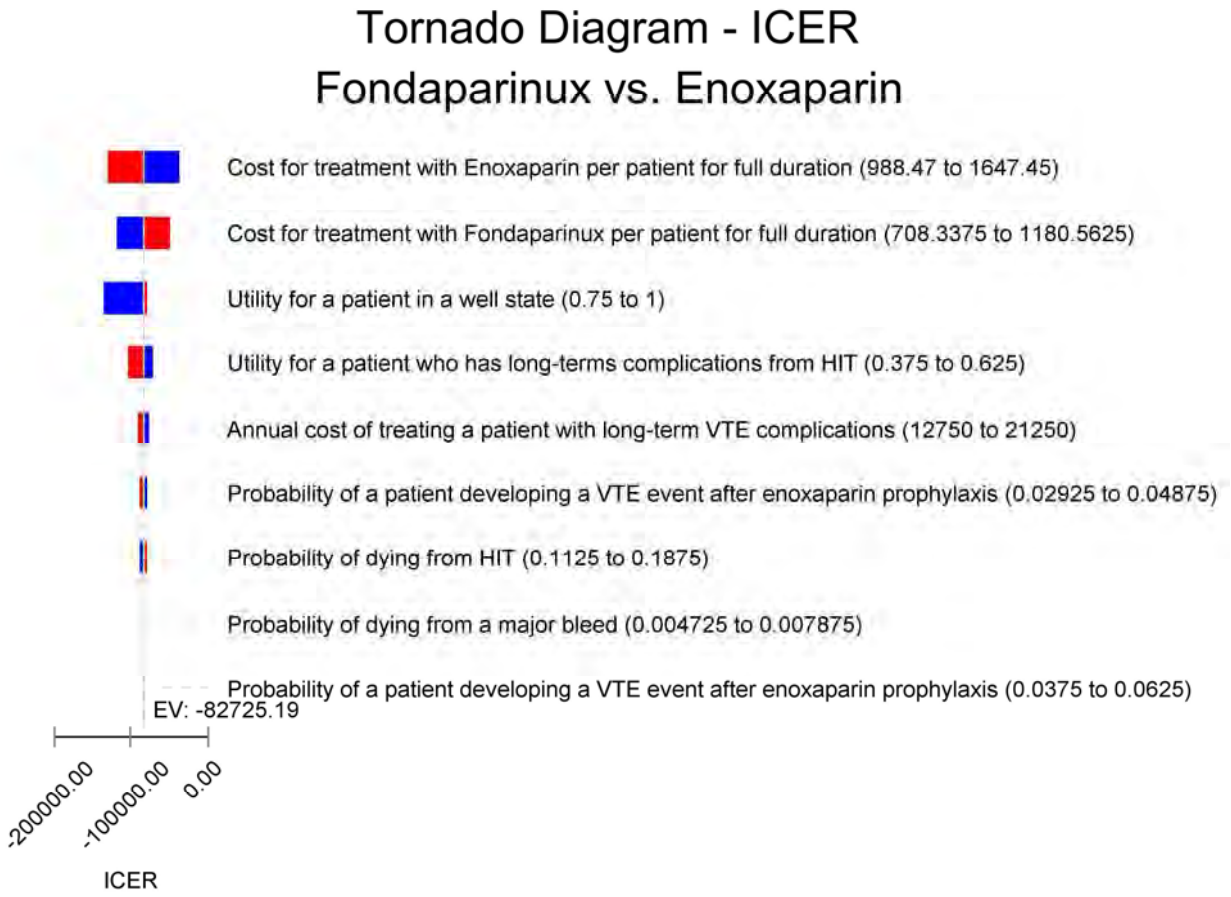


**Figure 4 One-way sensitivity analysis on key input parameters (fondaparinux versus enoxaparin)**

## b. Budget Impact Analysis

The base case analysis use of fondaparinux in prophylaxis of VTE would have an estimated incremental annual saving of R0.6 million to the pharmaceutical budget compared to enoxaparin.

| Patients accessing treatment | | 295<br>10% | 1,477<br>50%<br>(base case) | 2,362<br>80% | 2,953<br>100% |
|---|---|---|---|---|---|
| Price of fondaparinux/ 7.5 mg | 100% of SEP (R317) | ZAR 0,9 | ZAR 4,7 | ZAR 7,5 | ZAR 9,4 |
| | 75% of SEP (R238) | ZAR 0,6 | ZAR 3,1 | ZAR 4,9 | ZAR 6,2 |
| | 50% of SEP (R158) | ZAR 0,3 | ZAR 1,4 | ZAR 2,3 | ZAR 2,9 |
| | 20% of SEP (R63) | - ZAR 0,1 | - ZAR 0,5 | - ZAR 0,8 | - ZAR 1,0 |
| | 10% of SEP (R32) | - ZAR 0,2 | - ZAR 1,2 | - ZAR 1,9 | - ZAR 2,4 |

**Table 12. BIA of incremental pharmaceutical procurement cost of fondaparinux vs enoxaparin at different assumptions of treatment access and fondaparinux price (in ZAR millions)**

Key parameters driving budget impact to the South African public health pharmaceutical budget are likely to be assumptions relating to the price that can be achieved for fondaparinux, and the proportion of patients who access VTE treatment. This variation is shown in Table 12 where incremental to enoxaparin, listing fondaparinux on the EML for the treatment of VTE can range from a saving of R2.4 million (price 10% of SEP) to a cost of R9.4 million annually (price 100% of SEP) at 100% access.

# 7. Summary of international evidence on cost-effectiveness of fondaparinux

A comprehensive review of existing economic evidence and funding decisions by other national health technology assessment agencies was conducted.

Evidence reviewed

Shorr et al (2007) conducted a cost-minimization analysis comparing fondaparinux to enoxaparin for acute anticoagulation in deep vein thrombosis (DVT)[16]. They modelled a cohort of 1,000 hypothetical subjects and drew estimates for model inputs from the published literature. The relative treatment costs used were US$50 per course for fondaparinux, and US$84 per course for enoxaparin (ratio of 1:0.6)

Results

In the base case, total disease management costs per patient with fondaparinux were $US 472 compared to $US 769 with enoxaparin. The 95% CI around this difference ranged from $US 48 to $US 401. The model was mildly sensitive to the pharmacy acquisition costs of fondaparinux and enoxaparin, which was the major driver of overall costs. Neither the rates of nor costs associated with DVT recurrence, major bleeding, nor HIT substantially affected the observations. The authors conclude that from a healthcare

[16] Shorr AF, Jackson WL, Moores LK, Warkentin TE. Minimizing costs for treating deep vein thrombosis : the role for fondaparinux. J Thromb Thrombolysis. 2007;23:229–36

system perspective, fondaparinux use offers an attractive economic alternative to other agents for initial DVT therapy.

## 8. International reccomendations

**National Institute for Health and Care Excellence (England and Wales)**

A formal technology appraisal of fondaparinux has not been conducted by NICE. However, Clinical Guideline NG89: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism[17] recommends the following:

- for patients with confirmed proximal DVT or PE a LMWH (e.g. enoxaparin) or fondaparinux should be offered.
- for patients with an increased risk of bleeding or who are haemodynamically unstable, UFH should be considered,
- for patients with severe renal impairment or established renal failure offer unfractionated heparin (UFH) with dose adjustments based on the APTT or LMWH with dose adjustments based on an anti-Xa assay.

**Scottish Medicines Consortium (SMC, Scotland)**

In guidance issued by the SMC in 2006, fondaparinux is not recommended for use within NHS Scotland for the treatment of VTE as the manufacturer did not made a submission to SMC regarding this product in this indication [18].

In guidance issued in 2002, the SMC notes that fondaparinux is predicted to be a cost-effective alternative to enoxaparin in a robust economic model and that fondaparinux may be considered for patients for whom antithrombotic therapy is appropriate, recognising that other antithrombotic agents and other approaches to prophylaxis may be more suitable in some situations[19].

**Pharmaceutical Benefits Scheme (Australia)**

- Fondaparinux is not approved for the treatment of VTE
- Enoxaparin is listed for all registered indications without restricted access (with exception of special restricted benefit for use in haemodialysis).

[17] National Institute for Health and Care Excellence. NICE Guideline NG89: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018. https://www.nice.org.uk/guidance/ng89/resources/venous-thromboembolism-in-over-16s-reducing-the-risk-of-hospitalacquired-deep-vein-thrombosis-or-pulmonary-embolism-pdf-1837703092165

[18] Scottish Medicines Consortium. Fondaparinux (Arixtra) | Treatment of acute deep vein thrombosis and the treatment of acute pulmonary embolism. 2006. https://www.scottishmedicines.org.uk/media/1749/fondaparinux_arixtra_dvt__262-06_.pdf

[19] Scottish Medicines Consortium. Fondaparinux (Arixtra) | Antithrombotic therapy. 2002. https://www.scottishmedicines.org.uk/media/1750/fondiparinuxadvice_8-11-02_.pdf

# 9. Discussion

Key limitations in the assessment include the extent to which the underlying clinical inputs are reflective of South African clinical practice and outcomes. This assessment makes a simplifying assumption that the treatment effect of fondaparinux as observed in clinical trials will be broadly applicable to the South African setting.

Further, the budget impact analysis is sensitive to the proportion of patient who actually receive treatment for VTE, however, compared to other uses of fondaparinux, at 3,000 patients the treatment indication is likely to be the lowest risk investment.

A key driver of costs is the assumption made around the price that is able to be achieved in a national tender for fondaparinux. The existing weighted national contract price for enoxaparin is 20% of the current Single Exist Price (SEP). A critical assumption of the base case analysis is that the National Department of Health will be able to achieve a similar reduction from the existing fondaparinux SEP when securing the national tender price of fondaparinux.

An additional key driver of costs and effects sis the immediate risk of death and long-term complications of developing HIT. Under a resource constrained environment such as the South African public health sector, staffing levels may limit frequent monitoring of all patients leading to greater risk of HIT with enoxaparin than is observed in the literature. This is likely to increase the difference in costs and effects between fondaparinux and comparators.

The cost effectiveness analysis indicates that fondaparinux yields greater health (in QALYs) at a lower net cost than enoxaparin. In this situation, an estimate of the appropriate threshold for the South African system is not required as it is estimated that fondaparinux dominates the comparators.

# Appendix III

## Main source of clinical inputs:

### *Indication treatment for VTE (as informed by Motivation to PPTC)*[20]


1. Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-analysis. JAMA. 2014;312(11):1122–35.
2. Akl E, Kahale L, Neumann I, Barba M, Sperati F, Terrenato I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer (Review). Cochrane Database Syst Rev. 2014;(6):Art. No.: CD006649.
3. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. New England Journal of Medicine. 2003;349:1695–702.
4. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Article Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Venous Thrombosis. Ann Intern Med. 2004;140:867–73.
5. Nakamura M, Okano Y, Minamiguchi H, Munemasa M, Sonoda M, Yamada N, et al. Multidetector-Row Computed Tomography-Based Clinical Assessment of Fondaparinux for Treatment of Acute Pulmonary Embolism and Acute Deep Vein Thrombosis in Japanese Patients. Circ J. 2011;75:1424–32.
6. Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD003074.


[20] Informed by Griesel R, Ntsekhe M, Motivation for Application to Provincial Pharmacy and Therapeutics Committee (Appendix I)

## Appendix IV

Conflicts of interest declared by Adult ERC members providing clinical advice for these costing analyses; assessed by the Chairperson[21]:

| Committee member | Name of Organisation | Nature of what was received | Classification of COI* |
|---|---|---|---|
| Prof P Commerford | • GSK | • Served on steering committee of the trials evaluating fondaparinux (OASIS) in CV disease and was a co-author on some of the papers. My institution received payment for conducting the studies. | Clearly significant |
| Dr R Griesel | • UCT | • Involved in drafting the initial motivation for fondaparinux, submitted to the Western Cape PTC. | Potentially significant |

[21] Minutes of the Adult Hospital Level Committee meeting, 19 April 2018