South African National Essential Medicines List
Adult Hospital Medication Review Process

COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSES

Fondaparinux for the **prophylaxis of venous thromboembolism** in medical and surgical 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 and budget impact analysis attempts to make reasonable estimations of the budget impact and cost-effectiveness of the use of fondaparinux in the prophylaxis of venous thromboembolism (VTE) compared to existing treatments in the South African public health system. 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 fondaparinux on in the Adult Hospital Standard Treatment Guideline (AHSTG) and the National Essential Medicines List (EML).

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

Based on current procurement department of health national procurement volumes, it is estimated that approximately 500,000 patients annually receive prophylaxis for VTE with the existing treatments (enoxaparin or unfractionated heparin) in the South African public health system annually[3]. It is unknown how many patients would potentially receive VTE prophylaxis under a full access to treatment scenario, however a 2017 report by Rayne et al [4] estimated that there are 5,227 surgeries per 100,000 population in South Africa, adjusted for the public sector only this would be almost 1.5 million surgical procedures annually. Accounting for potential medical patients indicates that current access to VTE prophylaxis is below one quarter of patients who would gain access under existing STG recommendations.

Concurrent to this assessment, the use of fondaparinux is also being considered in the treatment 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 available for use in South Africa. The MCC-licenced indications for fondaparinux and comparators unfractionated heparin (UFH) and enoxaparin related to VTE prophylaxis are listed in table 1. Fondaparinux is not currently licenced for use in medical patients at risk of VTE[5].

UFH	Enoxaparin	Fondaparinux
Prophylactically after surgery to prevent thrombo-embolic complications[6].	To reduce the risk of post-operative VTE in high-risk patients (e.g. orthopaedic surgery) and moderate-risk patients (e.g. abdominal surgery[7]).	To reduce the risk of VTE in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery To reduce the risk of VTE in patients undergoing abdominal surgery who are at risk of thromboembolic complications

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

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

[3] Contract Circular HP06-2017SVP
[4] Rayne S, et al. BMJ Glob Health 2017;2:e000170. doi:10.1136/bmjgh-2016-000170
[5] South African package insert and patient information leaflet for fondaparinux sodium: Pharmacare Limited Arixtra (hard copy)
[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)

Chapter of AH STG	Disorder	Indication
2. Blood and Blood Forming Organs	2.7 Anaemia, Sickle Cell	Prevention of venous thromboembolism in sickle-cell anaemia
	2.14 Venous Thromboembolism	Prophylaxis of proximal venous thrombosis and/or pulmonary embolism for most patients undergoing surgery
3. Cardiovascular	3.4 Congestive Cardiac Failure (CCF)	Prevention of deep vein thrombosis in congestive heart failure patients admitted to hospital
6. Obstetrics	6.3 Heart Disease in Pregnancy	Prophylaxis for venous thromboembolism in pregnancy
8. Endocrine	8.6.2 Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic State	Treatment in diabetic ketoacidosis and hyperosmolar hyperglycaemic state
9. Systemic and Healthcare - Associated Infections	9.7 Tetanus	Prophylaxis for Deep Vein Thrombosis in patients with Tetanus
14. Neurological Disorders	14.1.1 Stroke	Prophylaxis for Deep Vein Thrombosis in secondary prevention of stroke

Table 2. Listed indications for enoxaparin and UFH: 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[8] and the South African Guidelines for Pharmacoeconomic Analysis[9]. 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. The patient population is all medical and surgical patients at increased risk of VTE, and incorporates the sub-indications for prophylaxis of VTE in diabetic ketoacidosis, heart disease in pregnancy, CCF, sickle cell anaemia, stroke, and tetanus.

Indication	Population	Intervention	Comparator	Outcomes	Perspective
Prophylaxis of VTE	All adult medical and surgical patients at increased risk of VTE	fondaparinux	*Base case:* enoxaparin *Additional* UFH	• VTE occurrence • Major bleed • Death • QALYs • Total cost to health system (annual and 5-year NPV) • 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 either enoxaparin or UFH in the prophylaxis of VTE in hospitalised medical and surgical patients (figure 1). Effects and costs were estimated for the immediate treatment

[8] 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.
[9] 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.

period, and extrapolated over a lifetime time horizon. The model consists of a decision tree for the initial inpatient stay where either fondaparinux, enoxaparin or UFH is administered. During admission, patients are at risk of a major bleed and/or a VTE event. To capture progression following discharge, a Markov-model structure was developed where each year, patients will move into either a state of otherwise well (survive), well with VTE-related complications (survive with complications) or die. The Markov model is then run for 50 years, at which time 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 or major bleed.

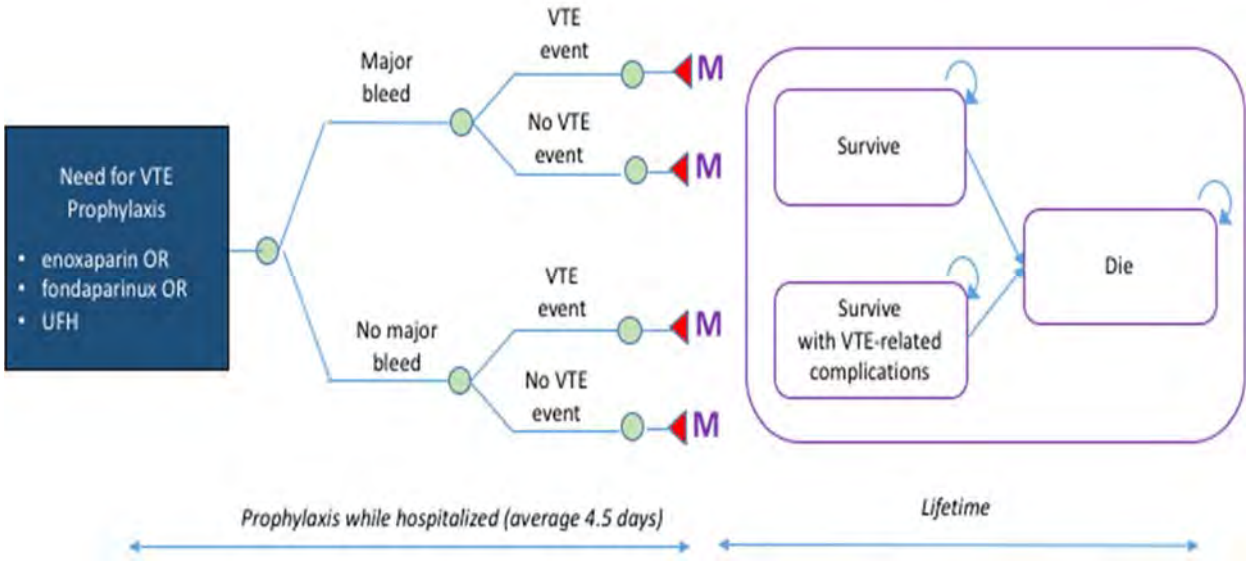

Figure 1. Decision analytic model structure to estimate cost effectiveness of fondaparinux in VTE prophylaxis

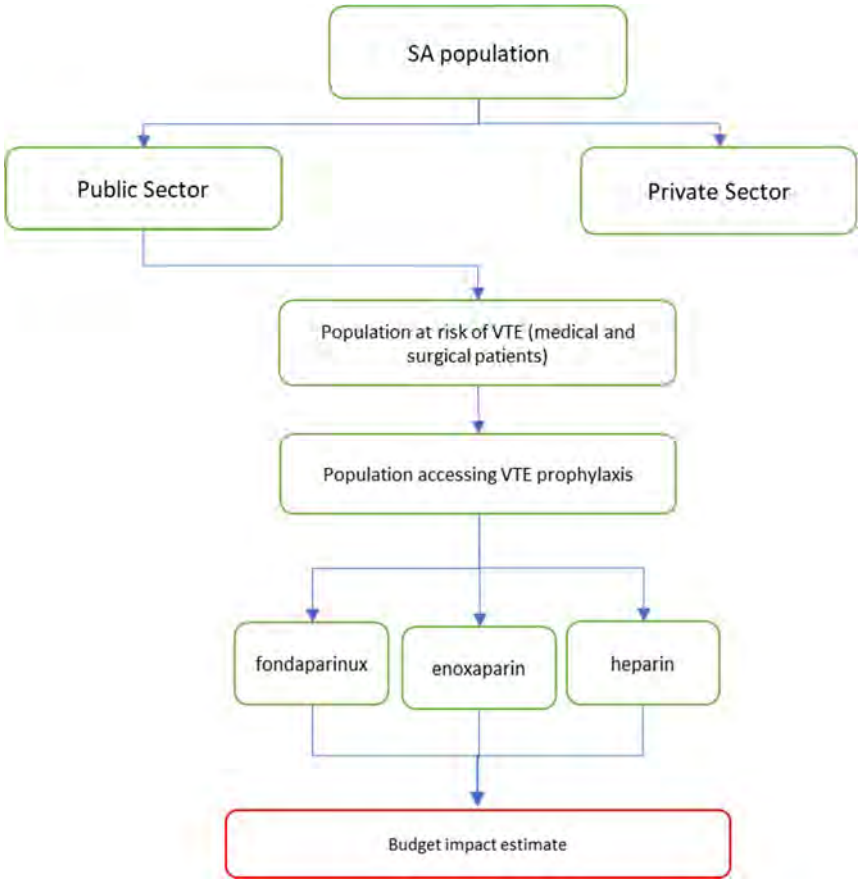

Figure 2. Framework to estimate budget impact of introducing fondaparinux to the South African health system in VTE prophylaxis

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 prophylaxis of VTE in as an alternative to UFH or enoxaparin. The budget impact estimate is based on the annual procurement cost if the entire existing patient population who accesses VTE prophylaxis switched to fondaparinux. In reality, local prescribing preference, interpatient variability and market supply would result in a proportion of the market switching from either UFH or enoxaparin to fondaparinux, however the presentation of this extreme scenario is likely to provide some indication of the expected upper limit of the budget impact at the level of the Essential Drugs Program. In addition, the budget impact represents only those patients who would access the public health system, and is modified by those who are likely to access treatment, as informed by existing volumes of enoxaparin prophylaxis-doses (40mg vial) procured under national tender. Key assumptions about expected national contract price and patients accessing treatment are 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 trials 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
Dong, K 2016	Systematic Review	A Cochrane systematic review evaluating fondaparinux, enoxaparin and warfarin. Main outcome of interest was incidence of Venous Thromboembolism (VTE) which was higher in enoxaparin (0.11) than fondaparinux (0.059). Major bleed was the main safety outcome which was higher for fondaparinux (0.025) than for enoxaparin (0.018). Mortality outcomes were death from major bleed (fondaparinux = 0.0004; enoxaparin = 0.0006) and death from PE (fondaparinux = 0.009; enoxaparin = 0.0013).
Akl *et al.* 2014	Systematic Review	A Cochrane systematic review evaluating low molecular weight heparin (LMWH) and unfractionated heparin (UFH) in cancer patients receiving thromboprophylaxis. Main outcome of interest was incidence of pulmonary embolism (PE) which favoured LMWH over fondaparinux, 0.003 versus 0.007 respectively.
Alikhan *et al*. 2014	Systematic review	A Cochrane systematic review evaluating unfractionated heparin (UFH) compared to placebo and LMWH. Incidence of Deep Vein Thrombosis (DVT) was 0.051 for LMWH and 0.065 for UFH. Incidence of PE was lower for LMWH (0.003) compared to UFH (0.004). Main safety outcome was major bleed and UFH had an incidence of 0.01. Mortality rates were 0.009 due to major bleed and 0.006 due to PE.

Table 4. Pivotal trials and reviews – prophylaxis 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, enoxaparin or UFH relating to progression to a VTE, suffering a major bleed, and death. A key assumption made due to limited evidence is that UNF is non-inferior to enoxaparin for the probability of VTE.

Description	Value	Lower value	Upper value	Source
Probability of VTE fondaparinux	0.059	0.04425	0.07375	Dong *et al.* 2016
Probability of VTE enoxaparin	0.110	0.0825	0.1375	Dong *et al.* 2016
Probability of VTE UFH	0.110	0.0825	0.1375	Alikhan *et al*. 2014[10]
Probability of Major Bleed fondaparinux	0.025	0.01875	0.03125	Dong *et al.* 2016
Probability of Major Bleed enoxaparin	0.018	0.0135	0.0225	Dong *et al.* 2016
Probability of Major Bleed UFH	0.012	0.007	0.017	Alikhan *et al*. 2014
Probability Death with PE	0.0013	0.000975	0.001625	Dong *et al.* 2016[11]
Probability Death with Major Bleed	0.0006	0.00045	0.00075	Dong *et al.* 2016[12]

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 (otherwise well) or surviving with complications post VTE (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	0.72	1
Survival (with complications)	0.7	0.525	0.875
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 (recurring transitions between the long-term states). For example, the probability that a patient will move from "Survival with VTE complications" to dead in any one year is 0.0313. In this model, it is assumed that patients would not move between Survival (no long-term complications) and Survival (post VTE) as VTE is assumed to have occurred at the point of hospitalisation or shortly after discharge.

Markov state transition (long term) probabilities

	Survival without complications	Survival with VTE complications	Dead
Survival without complications	0.97	0	0.03
Survival with VTE complications	0	0.9687	0.0313
Dead	0	0	1

Table 7. Transition probabilities between long-term Markov states

The central assumptions for the model are that

- Patient enters Markov transition model after completion of 4.5 days prophylaxis, directly after discharge

[10] Assumed to be no worse than enoxaparin
[11] Assumed to be the same across all drugs
[12] Assumed to be the same across all drugs

- UFH is assumed to be non-inferior to enoxaparin for risk of VTE.
- The quality of life of a patient who is discharged without experience a VTE is 0.96 – i.e. the person is at almost full health
- Each transition state has a one year cycle length
- A patient does not experience any long-term complications as a result 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 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[13].

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

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

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

Medicine	Dosage	Formulation	Unit cost	Number of units daily	Medicine cost (per day)	Administration Cost (per day)	Average treatment duration (days)	Total Cost for treatment
fondaparinux	SC, 2.5mg/0.2ml daily	2.5mg	R41.58	1	R41.58	R9.95	4.5	R231.90
enoxaparin	SC, 40mg daily	40mg/0.4ml	R27.70	1	R27.70	R9.95	4.5	R169.43
UFH	SC, 5000 IU, 12 hourly	5000IU/mL, 5ml vial	R24.85	0.4	R9.94	R14.03	4.5	R107.86

Table 10. Medicine regimen costs

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, and four minutes nurse time for UFH. 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 11 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 prophylaxis of enoxaparin per patient	R 169.43	R127	R212	Contract Circular[14] HP06-2017SVP
Cost for prophylaxis of fondaparinux per patient	R 231.90	R174	R290	See Tables 8 -10
Cost for prophylaxis of UFH per patient	R 107.86	R89	R135	Contract Circular HP06-2017SVP
Cost of treating a major bleed	R 11 268	R8 451	R14 085	UPFS 2017[15]
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
Recurring Costs (annual)				
Costs of treating a patient post VTE	R17 000	R12 750	R21 250	UPFS 2017
Costs of patient that survives without suffering a VTE	R500	R375	R625	UPFS 2017

Table 11. Model cost inputs

[14] http://www.health.gov.za/index.php/medicine?download=2649:master-procurement-catalogue-05-february-2018
[15] South African Uniform Patient Fee Schedule. National Department of Health 2017

6. Results

a. Cost effectiveness analysis

The resultant Incremental Cost Effectiveness Ratios (ICERs) are in Table 10. Listing fondaparinux for prophylaxis of VTE is expected to yield greater health gains, at a lower overall price compared to both UFH and enoxaparin. UFH and enoxaparin are therefore considered to be dominated. The price of fondaparinux used in the CEA is 20% of the current SEP (R48.51 per unit).

Strategy	Cost	Incr Cost	QALYs	Incr QALYs	Incr C/E
Fondaparinux	R15,082	0	23,88	0	0
UFH	R16,416	R1,334	23,88	-0,005	Dominated
Enoxaparin	R16,541	R1,459	23,87	-0,001	Dominated

Table 10. Summary of cost effectiveness of fondaparinux in the prophylaxis of VTE

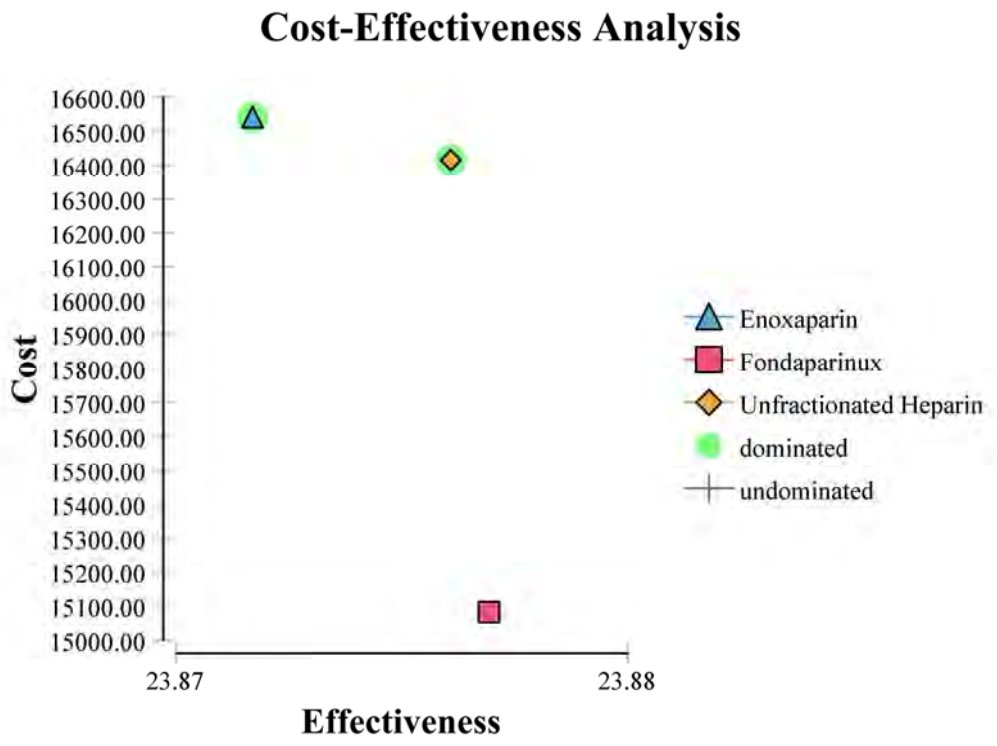

Figure 3: Cost-effectiveness graph VTE prophylaxis

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), and Figure 5 (fondaparinux vs UFH). 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 probability of major

bleed following prophylaxis with fondaparinux or enoxaparin has the largest individual impact on the result, however this does not change the finding that fondaparinux dominates comparators.

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

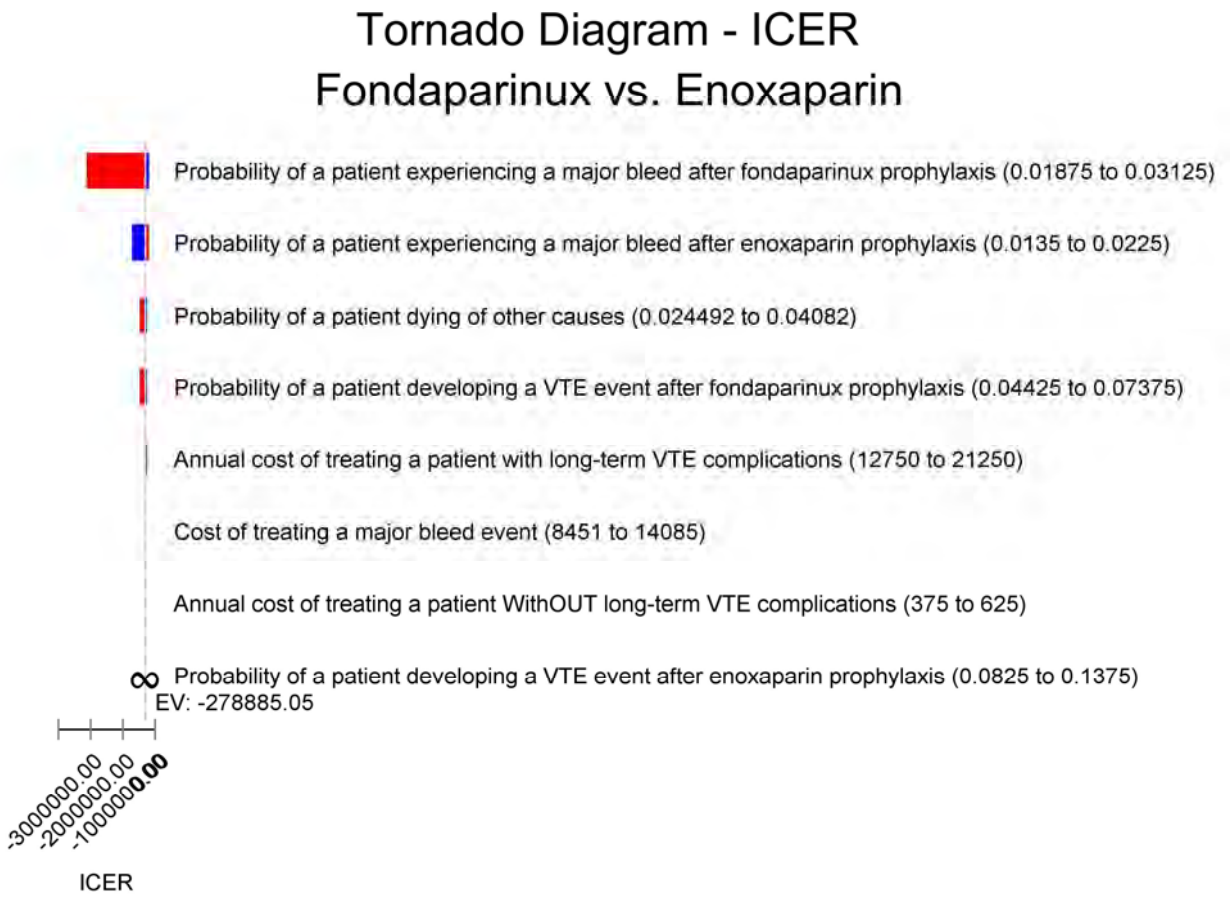

Figure 4 One-way sensitivity analysis on key input parameters fondaparinux vs enoxaparin

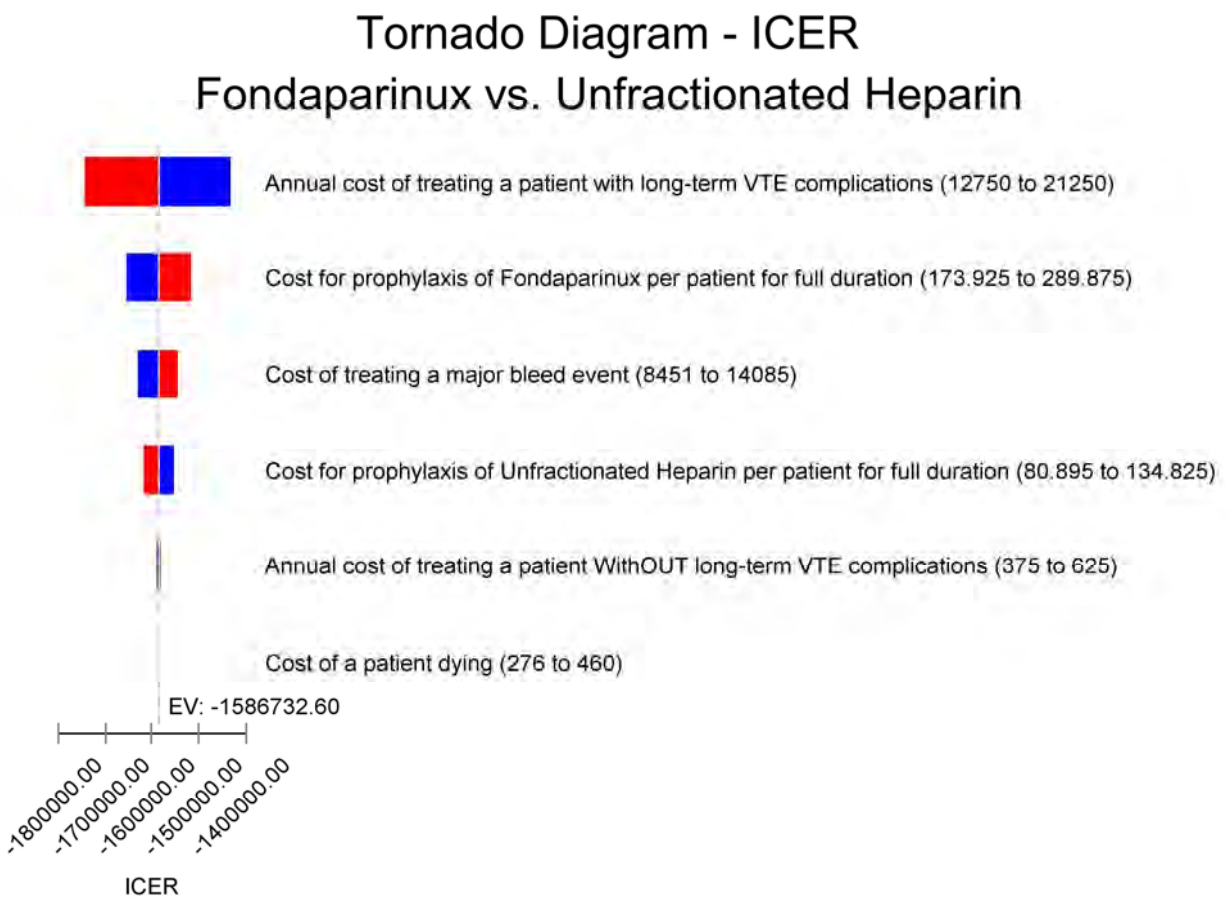

Figure 5 One-way sensitivity analysis on key input parameters fondaparinux vs UFH

b. Budget Impact Analysis

The use of fondaparinux in prophylaxis of VTE compared to the current national tender price of enoxaparin would have an estimated incremental annual pharmaceutical procurement cost of R15.2 million under the base case scenario that 50% of patients who may benefit from prophylaxis receive treatment, and the national tender price achieved for fondaparinux is 20% of the current Single Exit Price (SEP). These base case values are chosen based on current procurement volumes of enoxaparin to indicate currently treated patients, and that the national tender price for enoxaparin is currently 20% of its SEP (Table 11).

Patients accessing treatment		48,723 10%	243,614 50% (base case)	389,782 80%	487,227 100%
Price of fondaparinux/ 2.5 mg	100% of SEP (R207.91)	ZAR 39,5	ZAR 197,6	ZAR 316,1	ZAR 395,1
	75% of SEP (R155,93)	ZAR 28,1	ZAR 140,6	ZAR 224,9	ZAR 281,2
	50% of SEP (R103,96)	ZAR 16,7	ZAR 83,6	ZAR 133,8	ZAR 167,2
	20% of SEP (R41,58))	ZAR 3,0	ZAR 15,2	ZAR 24,3	ZAR 30,4
	10% of SEP (R20,79)	-ZAR 1,5	-ZAR 7,6	-ZAR 12,1	-ZAR 15,1

Table 11. BIA of Incremental pharmaceutical procurement cost (in ZAR millions) of fondaparinux vs enoxaparin at different assumptions of treatment access and fondaparinux price

The use of fondaparinux in prophylaxis of VTE compared to the current national tender price of enoxaparin would have an estimated incremental annual health system saving of R 267.1 million under the base case scenario described above. As the health system cost estimates take into account hospital management of unwanted clinical effects and medicine administration, the use of fondaparinux is expected to be cost saving at all estimates of potential price of fondaparinux, including at 100% of the current SEP (Table 12). The pharmaceutical procurement BIA and health system BIA is shown for fondaparinux compared to UFH under the same fondaparinux pricing and patient access assumptions is shown in tables 13 and 14 below.

Patients accessing treatment		48,723 10%	243,614 50% (base case)	389,782 80%	487,227 100%
Price of fondaparinux/ 2.5 mg	100% of SEP (R207.91)	-ZAR 17,9	- ZAR 89,4	- ZAR 143,1	- ZAR 178,9
	75% of SEP (R155,93)	- ZAR 29,3	- ZAR 146,4	- ZAR 234,3	- ZAR 292,9
	50% of SEP (R103,96)	- ZAR 40,7	- ZAR 203,4	- ZAR 325,5	- ZAR 406,8
	20% of SEP (R41,58))	- ZAR 54,4	- ZAR 271,8	- ZAR 434,9	- ZAR 543,6
	10% of SEP (R20,79)	- ZAR 58,9	- ZAR 294,6	- ZAR 471,3	- ZAR 589,2

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

Patients accessing treatment		48,723 10%	243,614 50% (base case)	389,782 80%	487,227 100%
Price of fondaparinux/ 2.5 mg	100% of SEP (R207.91)	ZAR 43,4	ZAR 217,0	ZAR 347,2	ZAR 434,1
	75% of SEP (R155,93)	ZAR 32,0	ZAR 160,0	ZAR 256,1	ZAR 320,1
	50% of SEP (R103,96)	ZAR 20,6	ZAR 103,1	ZAR 164,9	ZAR 206,1
	20% of SEP (R41,58))	ZAR 6,9	ZAR 34,7	ZAR 55,5	ZAR 69,4
	10% of SEP (R20,79)	ZAR 2,4	ZAR 11,9	ZAR 19,0	ZAR 23,8

Table 13. BIA of incremental pharmaceutical procurement cost (in ZAR millions) of fondaparinux vs UFH at different assumptions of treatment access and fondaparinux price

Patients accessing treatment		48,723 10%	243,614 50% (base case)	389,782 80%	487,227 100%
Price of fondaparinux/ 2.5 mg	100% of SEP (R207.91)	- ZAR 7,8	- ZAR 39,0	- ZAR 62,5	- ZAR 78,1
	75% of SEP (R155,93)	- ZAR 19,2	- ZAR 96,0	- ZAR 153,6	- ZAR 192,0
	50% of SEP (R103,96)	- ZAR 30,6	- ZAR 153,0	- ZAR 244,8	- ZAR 306,0
	20% of SEP (R41,58))	- ZAR 44,3	- ZAR 221,4	- ZAR 354,2	- ZAR 442,8
	10% of SEP (R20,79)	- ZAR 48,8	- ZAR 244,2	- ZAR 390,7	- ZAR 488,3

Table 14. BIA of incremental health system cost (in ZAR million) of fondaparinux vs UFH at different assumptions of treatment access and fondaparinux price

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.

6 articles investigating the cost-effectiveness of fondaparinux versus enoxaparin in venous thromboembolism (VTE) prevention among patients undergoing major orthopaedic surgery were reviewed. A summary of the publications included in the evidence review are presented in Table 15.

First author, publication year and country	Population	Intervention	Comparator	Outcome
Gordois, 2003, UK [16].	Patients undergoing total hip replacement, TKR or hip fracture surgery	fondaparinux	enoxaparin	Treatment costs per patient, and incidence of clinical VTE and VTE-related deaths
Lundkvist, 2003, Sweden [17].	Patients undergoing major orthopaedic surgery (TKR, total hip replacement or hip fracture surgery)	fondaparinux	enoxaparin	Cost per VTE prevented
Sullivan, 2004, US [18].	US patients undergoing major orthopaedic surgery	fondaparinux	enoxaparin	Rates of symptomatic thromboembolic events and healthcare costs
Dranitsaris, 2004, Canada [19]	Canadian patients undergoing major hip or knee surgeries	fondaparinux	enoxaparin	Number of symptomatic VTE events avoided, VTE incidence by day 11, Cost savings
Bjorvatn, 2005, Norway [20]	55 000 Patients undergoing orthopaedic surgery	fondaparinux	enoxaparin	Expected incidence of VTE and VTE-related deaths, and expected costs of VTE-related care

[16] Gordois, A., J. Posnett, L. Borris, P. Bossuyt, B. Jönsson, E. Levy, and G. De Pouvourville. "The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery." Journal of Thrombosis and Haemostasis 1, no. 10 (2003): 2167-2174.

[17] Lundkvist, Jonas, David Bergqvist, and Bengt Jönsson. "Cost-effectiveness of fondaparinux vs. enoxaparin as venous thromboembolism prophylaxis in Sweden." The European Journal of Health Economics, formerly: HEPAC 4, no. 4 (2003): 254-262.

[18] Sullivan, Sean D., Bruce L. Davidson, Susan R. Kahn, James E. Muntz, Gerry Oster, and Gary Raskob. "A cost-effectiveness analysis of fondaparinux sodium compared with enoxaparin sodium as prophylaxis against venous thromboembolism." Pharmacoeconomics 22, no. 9 (2004): 605-620.

[19] Dranitsaris G, Kahn S, Stumpo C, Paton T, Martineau J, Smith R, et al. Pharmacoeconomic Analysis of Fondaparinux Versus Enoxaparin for the Prevention of Thromboembolic Events in Othropaedic Surgery Patients. Am J Cardiovasc Drugs. 2004;4(5):325–33.

[20] Bjorvatn A, Kristiansen F. Fondaparinux Sodium Compared with Enoxaparin Sodium: a Cost-Effectiveness Analysis. Am J Cardiovasc Drugs. 2005;5(2):121–30

Capri, 2010, Italy [21].	Patients undergoing major orthopaedic surgery	fondaparinux	enoxaparin	Decreased VTE events, costs related to diagnosis, treatment and sequelae of the events.

Table 15. Brief description of publications investigating cost-effectiveness of fondaparinux in VTE prevention

Results

All of the studies concluded that fondaparinux is more effective and cost-saving compared with enoxaparin. This finding was stable when evaluated when key economic and clinical parameters were varied in all the studies apart from Gordois et al (2003) where the cost-effectiveness results were sensitive to the price differences between fondaparinux and enoxaparin, and variation in the rate of late deep vein thrombosis (DVT) and Bjorvatn et al (2005) were the results were also sensitive to the price differences between fondaparinux and enoxaparin.

A summary of the main findings from the publications included is presented in Table 16.

First author, publication year and country	Main Cost-Effectiveness Study Findings
Gordois, 2003, UK	Cost savings at 5 years was 27 GBP (USD $36) per patient (discounted at 6% per year). Fondaparinux was expected to produce 20 fewer clinical VTE events and 3.2 fewer VTE-related deaths per 1000 procedures at 5 years. Cost of anticoagulant therapy (daily dose): Fondaparinux 7.16 GBP, Enoxaparin 4.52 GBP (ratio 1.58)
Lundkvist, 2003, Sweden	Fondaparinux was cost saving and more effective than enoxaparin after total knee replacement and hip-fracture surgery and had costs per prevented venous thrombo-embolism of about 239 euros after total hip replacement.
Sullivan, 2004, US	The cost savings per patient of using fondaparinux over enoxaparin are $US61 at 30 days, $US89 at 3 months, and $US155 at 5 years. In the trial-based analysis, fondaparinux was estimated to prevent 15.1 symptomatic venous thromboembolic events (per 1000 patients) at 3 months compared with enoxaparin.
Dranitsaris, 2004, Canada	The model predicted that prophylaxis with fondaparinux would avoid an additional 16 symptomatic VTEs per 1000 patients over the first 90 days, with an average cost saving of $CAN55 per patient.
Bjorvatn, 2005, Norway	By day 90, fondaparinux is expected to avoid 180 more VTE events, and between 8 and 33 more VTE-related deaths per 10 000 patients than enoxaparin. Fondaparinux was also found to be cost saving in short term follow-up periods for hip fracture surgery. For extended follow-up periods fondaparinux was also likely to present the lower cost treatment option after total knee and hip replacement.
Capri, 2010, Italy	After 30 days of extended prophylaxis, fondaparinux was associated with a saving of €48.83 per patient; at the end of the first year, the saving increased to €72.13, and after 5 years, the savings were €74.36.

Table 16. Summary of findings from publications investigating cost-effectiveness of fondaparinux in VTE prevention

[21] Capri S, Ageno W, Imberti D, Palareti G, Piovella F, Scannapieco G, et al. Extended prophylaxis of venous thromboembolism with fondaparinux in patients undergoing major orthopaedic surgery in Italy : a cost-effectiveness analysis. Intern Emerg Med. 2010;5:33–40.

8. International recommendations

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[22] recommends that in the following patients, a LMWH (eg enoxaparin) should be used as first-line, and fondaparinux should only be used where a LMWH is contraindicated

- Acutely-ill medical patients
- Patients receiving palliative care
- Patients who are admitted to acute psychiatric ward
- Patients undergoing cardiac surgery (and who are not receiving any other anticoagulant therapy)
- Patients undergoing thoracic surgery

In the following patients, Clinical Guideline NG89 recommends that either a LMWH or fondaparinux can be given:

- Patients with lower-limb immobilisation
- Pre-operative patients (if surgery is delayed beyond the day of admission) and post-operative patients with fragility fractures of the pelvis, hip or proximal femur
- Patients undergoing abdominal surgery or bariatric surgery

Scottish Medicines Consortium (SMC, Scotland)

In guidance issued by the SMC in 2006, fondaparinux is not recommended for use within NHS Scotland for the prevention of VTE in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as those undergoing abdominal cancer surgery. The SMC notes that the economic case has not been demonstrated as fondaparinux showed non-inferiority to one other LMWH[23].

Fondaparinux is not recommended for use within NHS Scotland for the prevention of venous thromboembolic events (VTE) in medical patients who are judged to be at high risk of VTE and who are immobilised due to acute illness as the manufacturer did not made a submission to SMC regarding this product in this indication.[24].

Pharmaceutical Benefits Scheme (Australia)

- Restricted access granted for the use of fondaparinux in prevention of VTE only if patient is undergoing major hip surgery or a total knee replacement[25].
- Enoxaparin is listed for all registered indications without restricted access (with exception of special restricted benefit for use in haemodialysis).

[22] 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
[23] Scottish Medicines Consortium. Fondaparinux (Arixtra) |Prevention of Venous Thromboembolic Events. 2006. https://www.scottishmedicines.org.uk/media/1753/fondaparinux_arixtra_287_06.pdf
[24] Scottish Medicines Consortium. Fondaparinux (Arixtra) | Prevention of venous thromboembolic events. 2006. https://www.scottishmedicines.org.uk/media/1748/fondaparinux_arixtra_vte__261-06_.pdf
[25] http://www.pbs.gov.au/medicine/item/8775W

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 analysis makes a simplifying assumption that the prophylactic effect of fondaparinux as observed in clinical trials will be broadly applicable for all indications where enoxaparin is currently listed in the AHSTG, including all medical and surgical patients, and specific sub-indications including congestive heart failure, heart disease in pregnancy, diabetic ketoacidosis, tetanus, and sickle-cell anaemia.

A key driver of costs is the assumption made around the contract 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.

Further, the budget impact analysis is sensitive to the proportion of hospitalised medical and surgical patients who are at risk of developing a VTE who actually receive prophylaxis. The base case annual pharmaceutical budget impact (fondaparinux at 20% of current SEP, compared to enoxaparin) is estimated to be R15.2 assuming 50% of indicated patients could gain access to prophylaxis, but this ranges from R3.0 to R30.4 million when access changes from 10% to 100% respectively.

However, this investment is likely to be good value for money in South African context, as the cost effectiveness analysis indicates that fondaparinux yields similar health (in QALYs) at a lower net cost than enoxaparin or UFH. 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[26]

Indication Prophylaxis for VTE

1. Dong K, Song Y, Li X, Ding J, Gao Z, Lu D, et al. Pentasaccharides for the prevention of venous thromboembolism (Review). Cochrane Database Syst Rev. 2016;(10):Art. No.: CD005134.
2. Alikhan R, Forster R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). Cochrane Database of Systematic Reviews 2014. Issue 5. Art. No.: CD003747. DOI: 10.1002/14651858.CD003747.pub4.
3. Akl EA, Kahale LA, Sperati F, Neumann I, Labedi N, Terrenato I, Barba M, Sempos EV, Muti P, Cook D, Schünemann H. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD009447. DOI: 10.1002/14651858.CD009447.pub2.

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

Appendix IV

Conflicts of interest declared by Adult ERC members providing clinical advice for the costing analyses; assessed by the Chairperson[27].

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

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