**South African National Essential Medicines List**
**Pharmacoeconomics and Budget impact analysis Update**
**Adult Hospital Level**
**Component: Cardiovascular conditions**

**Date**: 10 September 2017
**Medication**: Rivaroxaban
**Indication:** Treatment of recurrent deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thrombolic events (VTE)

## 1 INTRODUCTION

A motivation was initially received for rivaroxaban to be added to the EML for the following conditions;

- Post hip and knee surgery prophylaxis
- Treatment of DVT and pulmonary embolism
- Stroke prevention in treatment of non-valvular atrial fibrillation

A pharmacoeconomics similation was developed in December 2015 to determine the incremental cost effectiveness ratio (ICER) and budget impact (BIA) for the use of rivaroxaban in the treatment of DVT or PE and the prevention of recurrent VTE compared to standard of care.

This updated report describes the ICER and BIA based on updated costs (effective for the date of this report).

## 2 PHARMACOECONOMICS MODEL - METHODS

A cost-minimization approach was used but with differences in bleeding rates and hospitalization costs taken into consideration. The perspective was that of a third-party payer – i.e. Department of Health/Government and therefore only direct costs were included. The costs were modeled for 3, 6 and 12 months and therefore no discounting was required. A decision tree structure was used as per the figure below;

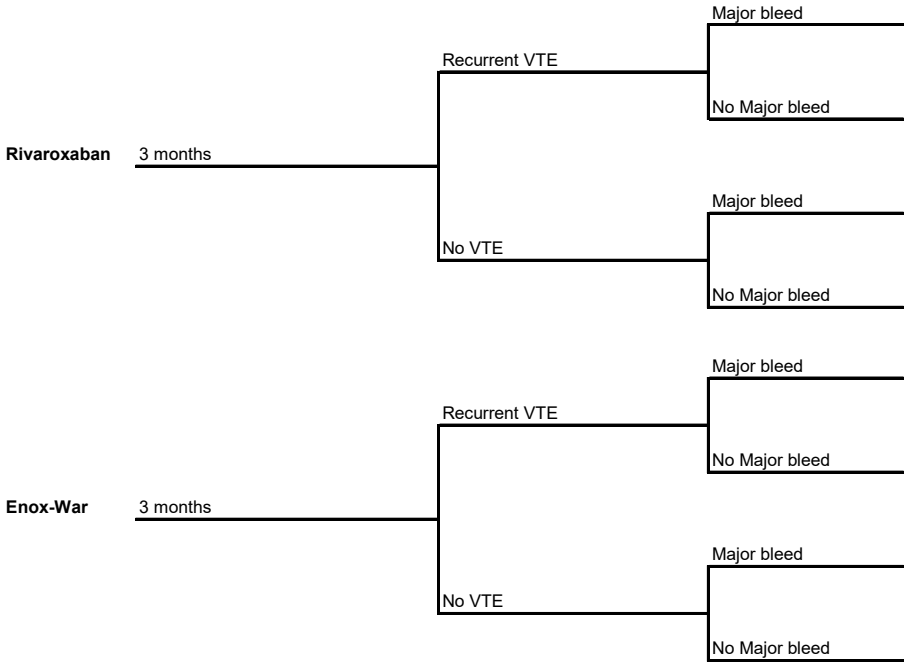


*Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin*

## 3 CLINICAL INPUTS AND COSTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources, predominantly the EINSTEIN-DVT and EINSTEIN-PE studies (1) (2) which showed a statistically significant non-inferiority in the primary efficacy endpoint (incidence of symptomatic recurrent VTE) in both trials at 3, 6 or 12 months and therefore a base-line event rate of recurrent symptomatic VTE was selected at 2.1%

The risk of first major bleeding was significantly reduced with rivaroxaban from 1.7% to 1% in the EINSTEIN pooled analysis (3).

The initial length of stay for treatment was based on 1 day in ICU followed by a general ward stay of 4 days and 5 days for rivaroxaban and enox/war respectively. Analysis of the EINSTEIN PE and DVT studies shows a reduction in initial length of stay for patients treated with rivaroxaban compared to standard of care (4).

The average length of stay for hospitalization for a recurrent VTE was taken from a review of the cost of VTE (5) in 18 published studies. The length of stay varied considerably between countries with ranges from 4.9-7 days and 5.8-7.7 days for DVT and PE respectively in the US. In Germany and Belgium the length of stay increased to around 14-24 days. Therefore a baseline LOS of 6 days was selected and a sensitivity analysis carried out to determine the impact.

The unit costs for in-patient admissions and consultations were taken from the UPFS Tariffs from April 2015. The medication costs for rivaroxaban were obtained from the SEP database and for warfarin/enoxaparin, the costs were obtained from the most recent contract database. INR monitoring costs were obtained from the 2015 NHLS Costing Tables.

The medicine costs used in the model are as follows;

**Medicine Costs**

| Medicine | Strength | Dosage form | Pack | Price/pack | Price /unit | SEP pack size | SEP (+VAT) | SEP (incl VAT)/unit |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rivaroxaban | 10 mg | tab | 30 | n/a | n/a | 30 | R 921.82 | R 30.73 |
| Rivaroxaban | 15 mg | tab | 42 | n/a | n/a | 42 | R 1 290.58 | R 30.73 |
| Rivaroxaban | 20 mg | tab | 28 | n/a | n/a | 28 | R 860.44 | R 30.73 |
| Warfarin | 5 mg | tab | 100 | R 60.82 | R 0.61 | 100 | R 125.15 | R 1.25 |
| Enoxaparin | 40mg | inj | 1 | R 27.70 | R 27.70 | | | |

*Table 1. Medicine pricing for rivaroxaban, enoxaparin and warfarin*

A number of assumptions were made for the model including the following;

- Hospitalisations included 1 day in ICU or HC followed by the balance of the days in general ward
- The patient was consulted by an ICU specialist once on the day in ICU followed by general medical consultations in the general ward per day thereafter. Only general ward or no hospital stay was also modelled.
- All patients were treated at a Level 2 facility in terms of costs
- Both DVT and PE patients were included together in the model even though it is acknowledged that they have different outcomes and prevalence.
- Recurrent VTEs were similar in terms of treatment regardless of whether the patient was on rivaroxaban or enoxaparin-warfarin and therefore accumulated the same costs
- Efficacy of rivaroxaban and standard of care is the same (proven by non-inferiority) based on EINSTEIN trials and only bleeding outcomes differ
- Only one further event occurred per time period (ie only one recurrent VTE regardless of whether in 3 6 or 12 months)
- Bleeding outcomes of rivaroxaban and standard of care differs (proven by pooled EINSTEIN data)
- All patients were admitted for treatment of recurrent DVT or PE

## 4 RESULTS

At a base case pricing of full SEP for rivaroxaban (R743 per month for 20mg), the incremental cost of treating a patient for 12 months with rivaroxaban would be approximately R2 500. The outcomes of the model were as follows;

| | ***3 months*** | ***6 months*** | ***12 months*** |
|---|---|---|---|
| ***Rivaroxaban*** | R 10 122.19 | R 13 549.58 | R 20 342.90 |
| ***Enoxaparin-Warfarin*** | R 8 036.89 | R 9 315.73 | R 10 387.20 |
| ***Incremental Cost*** | R 2 085.30 | R 4 233.85 | R 9 955.70 |

*Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 12 months*

If the price of rivaroxaban was reduced by 80%, the 3 and 6 month treatment periods would become cost-saving at -R66.75 and R-168.56 respectively.

The model was most sensitive to changes in LOS and then the price of rivaroxaban (Table 3). If patients did not need an ICU stay when on rivaroxaban, the model became cost-saving for at 3 months. However, if both rivaroxaban and enox-war had the same LOS, then the incremental cost increased quite substantially. Changing the efficacy event rate did not impact the model as much as varying the major bleed rate. Changing the LOS of a recurrent VTE did not impact the model at all as it was assumed to be the same for both arms (rivaroxaban and enox-war).

| | | **Incremental Cost** | | |
|---|---|---|---|---|
| **Model parameter** | **Range** | **3 months** | **6 months** | **12 months** |
| *Event Efficacy (VTE)* | *2.10%* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower (Riv) | 1.75% | R 2 056.13 | R 4 203.64 | R 9 923.42 |
| Upper (Enox-war) | 3.00% | R 2 010.30 | R 4 156.18 | R 9 872.69 |
| *Event Bleed riv* | *1%* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower | 0.5% | R 2 030.54 | R 4 179.09 | R 9 900.94 |
| No Diff | 1.7% | R 2 161.96 | R 4 310.51 | R 10 032.37 |

| | | | | |
|---|---|---|---|---|
| Upper | 2.5% | R 2 249.58 | R 4 398.13 | R 10 119.98 |
| *Event Bleed enox-war* | *1.70%* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower | 1.00% | R 2 161.96 | R 4 310.51 | R 10 032.37 |
| Upper | 3.00% | R 1 942.92 | R 4 091.47 | R 9 813.33 |
| *LOS_riv* | *5* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower | 4 | R 1 547.30 | R 3 695.85 | R 9 417.70 |
| Upper | 10 | R 4 775.30 | R 6 923.85 | R 12 645.70 |
| No ICU stay | 5 | -R 1 762.70 | R 385.85 | R 6 107.70 |
| *LOS_enox-war* | *6* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower | 5 | R 2 963.70 | R 4 771.85 | R 10 493.70 |
| Upper | 10 | -R 604.70 | R 1 543.85 | R 7 265.70 |
| No ICU stay | 5 | R 5 933.30 | R 8 081.85 | R 13 803.70 |
| *LOSre* | *8* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Any value | 5 | R 2 085.30 | R 4 233.85 | R 9 955.70 |
| *Rivaroxaban (per unit)* | *30.73* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| 20% reduction | 24.58 | R 1 397.02 | R 2 980.14 | R 7 583.43 |
| 50% reduction | 15.36 | R 364.50 | R 1 099.47 | R 4 024.90 |
| 65% reduction | 10.76 | -R 151.76 | R 475.62 | R 2 305.70 |
| 70% reduction | 9.22 | -R 323.85 | -R 154.31 | R 1 652.55 |
| 75% reduction | 7.68 | -R 495.94 | -R 467.76 | R 1 059.46 |
| 80% reduction | 6.15 | -R 668.03 | -R 781.20 | R 466.38 |
| *Major bleed Cost* | *5476.00* | *R 2 085.30* | *R 4 233.85* | *R 9 955.70* |
| Lower | 3000 | R 2 119.96 | R 4 268.51 | R 9 990.37 |
| Upper | 15000 | R 1 951.96 | R 4 100.51 | R 9 822.37 |

*Table 3. Sensitivity Analysis of key parameters for the model at 3, 6, and 12 months*

## 5 PUBLISHED HEALTH ECONOMICS

There are a number of published cost-effectiveness studies on this subject (6). All used efficacy data from the EINSTEIN DVT and PE studies and reported ICERS as cost/LYG and cost/QALY. Rivaroxaban was found to be dominant (ie cost less with greater benefit) in all 3 of the US based studies, as well as in the model submitted by the manufacturer to NICE in the UK. The Evidence Review Group (ERG) of NICE presented their own analysis for DVT and PE and found that for DVT rivaroxaban dominated standard of care in the 3 month treatment arm but showed an ICER of £3,200 and £14,900 for the 6 and 12 month treatment groups respectively. For PE, the ERG produced an ICER of £11,590/QALY for 12 months treatment and £35,909 for lifelong treatment. An analysis carried out in 2015 which evaluated the cost-effectiveness of treatment of VTE with rivaroxaban compared to LMWH/WAR for lifelong treatment showed ICERs of £8677 and £7072 for DVT and PE respectively which is still well below the cost-effectiveness threshold (around £20 000/QALY) for the UK (7).

## 6 BUDGET IMPACT ANALYSIS

It is challenging to determine the incidence of DVT and PE as well as rate of recurrence in the South African population. According to the South African guidelines, the DVT prevalence appears to be similar in medically ill patients compared to moderate risk surgery patients (around 10-20%) (8) however little information is available as to the actual numbers of DVTs or PE in the total population in order to be able to assess the total and incremental budget impact of treating patients with rivaroxaban compared to standard of care.

The total **medicine cost** per patient of treating DVT and PE with rivaroxaban compared to enoxaparin-warfarin (including INR monitoring) is shown in Table 4 below;

| **Rivaroxaban** | **Cost Rx** | | **Total Cost (including initial Tx and INR)** |
|---|---|---|---|
| Initial phase (15mg bd x 21 days) | R 1 290.58 | | |

| | | | |
|---|---|---|---|
| 3 months (20mg daily) | R 2 151.09 | | R 3 441.68 |
| 6 months (20mg daily) | R 4 978.25 | | R 6 268.83 |
| 12 months (20mg daily) | R 10 571.09 | | R 11 861.68 |
| **Enoxaparin+Warfarin** | | **INR** | |
| Initial phase (enox 160mg x 8 days) | R 886.40 | | |
| Initial phase (warfarin 5mg x 26 days) | R 15.81 | R 255.30 | R 1 157.51 |
| 3 months (5mg daily) | R 37.10 | R 85.10 | R 1 279.71 |
| 6 months (5mg daily) | R 93.05 | R 212.75 | R 1 463.32 |
| 12 months (5mg daily) | R 203.75 | R 468.05 | R 1 829.31 |

*Table 4. Medicine cost of treating DVT and PE for 3, 6, and 12 months*

The absolute medicine cost difference per patient is R2 284.16 (3 months), R4 989.12 (6 months) and R10 398.36 (12 months) assuming 6 INR in the initial treatment phase followed by 1 INR per month thereafter.

Making some broad assumptions around number of patients eligible for treatment, the possible incremental budget impact, as per the pharmacoeconomics model, could be as follows;

| ***Per patient*** | **Rivaroxaban** | **Enoxaparin-Warfarin + INR** | **Incremental cost** |
|---|---|---|---|
| 3 months | R 10 122.19 | R 8 036.89 | R 2 085.30 |
| 6 months | R 13 549.58 | R 9 315.73 | R 4 233.85 |
| 12 months | R 20 342.90 | R 10 387.20 | R 9 955.70 |
| ***1000 patients*** | | | |
| 3 months | R 10 122 190.10 | R 8 036 890.40 | R 2 085 299.70 |
| 6 months | R 13 549 579.87 | R 9 315 731.80 | R 4 233 848.07 |
| 12 months | R 20 342 899.57 | R 10 387 198.20 | R 9 955 701.37 |
| ***15 000 patients*** | | | |
| 3 months | R 151 832 851.50 | R 120 553 356.00 | R 31 279 495.50 |
| 6 months | R 203 243 698.07 | R 139 735 977.00 | R 63 507 721.07 |
| 12 months | R 305 143 493.57 | R 155 807 973.00 | R 149 335 520.57 |
| ***25 000 patients*** | | | |
| 3 months | R 253 054 752.50 | R 200 922 260.00 | R 52 132 492.50 |
| 6 months | R 338 739 496.79 | R 232 893 295.00 | R 105 846 201.79 |
| 12 months | R 508 572 489.29 | R 259 679 955.00 | R 248 892 534.29 |

*Table 5. Incremental cost (Rands) of treatment for rivaroxaban compared to enoxaparin-warfarin*

However, the pharmacoeconomics model shows that whilst there is an increase in medicine costs when rivaroxaban is used, in a number of instances, rivaroxaban becomes cost-saving compared to warfarin, especially when the price of rivaroxaban is reduced by 80% and when the LOS of rivaroxaban is reduced compared to standard of care and even more so if no ICU stay is required. Therefore it is possible that the introduction of rivaroxaban at a negotiated price reduction could be cost-neutral or even cost-saving from a budget impact perspective.

## 7 CONCLUSION

There is an incremental cost per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE, however, if the price of rivaroxaban is reduced, the incremental cost can be neutralized. A price reduction should be negotiated.

The initial budget impact will be considerable and it is recommended that a follow-up study is carried out to assess whether the projected cost savings from reduction in hospital stay and reduction in long-term outcomes (fewer bleeds, possibly fewer recurrent VTEs) materialize.

There is a risk that if rivaroxaban becomes available on the EML for the treatment of VTE, it will also be used in other clinical indications for anticoagulation, such as atrial fibrillation, where the cost-effectiveness is not proven.

## 8 REFERENCES


1. **Investigators, EINSTEIN-PE.** Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New England Journal of Medicine.* 2012, Vol. 366, pp. 1287-1297.

2. **Investigators, EINSTEIN.** Oral rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine.* 2010, Vol. 363, 26, pp. 2499-2510.

3. **Prins MH, Lensing AW, Bauersachs R et al.** Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J.* 2013.

4. **van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AW.** Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin.* 2014, Vol. 30, 5, pp. 829-837.

5. **Fernandez M, Hogue S, Preblick R, Kwong WJ.** Review of the cost of venous thromboembolism. *ClinicoEconomics and Outcomes Research.* 2015, Vol. 7, pp. 451-462.

6. **Burness C, Perry C.** Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. *Drugs.* 2014, Vol. 74, pp. 243-262.

7. **Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R.** Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. *Thrombosis Journal.* 2015, Vol. 13, p. 20.

8. **B F Jacobson, S Louw, H Büller, M Mer, P R de Jong, P Rowji , E Schapkaitz, D Adler, A Beeton, H-C Hsu, P Wessels, S Haas,.** Venous thromboembolism: Prophylactic and therapeutic practice guideline. *SAMJ.* 2013, Vol. 103, 4, pp. 260-267.