health
Department:
Health
REPUBLIC OF SOUTH AFRICA

National Essential Medicines List Pharmacoeconomics and Budget impact analysis Update
Adult Hospital Level
Component: Blood and blood forming organs

Date: 15 July 2020
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 simulation was developed in December 2015 to determine the incremental cost effectiveness ratio (ICER) and budget impact analysis (BIA) for the use of rivaroxaban in the treatment of DVT or PE and the prevention of recurrent VTE compared to standard of care.

The report was updated in September 2017 to reflect the updated ICER and BIA based on updated costs, and has been subsequently updated to describe costs effective for the date of this report, including a quotation from Bayer of a price 46% lower than SEP (8 July 2020).

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;

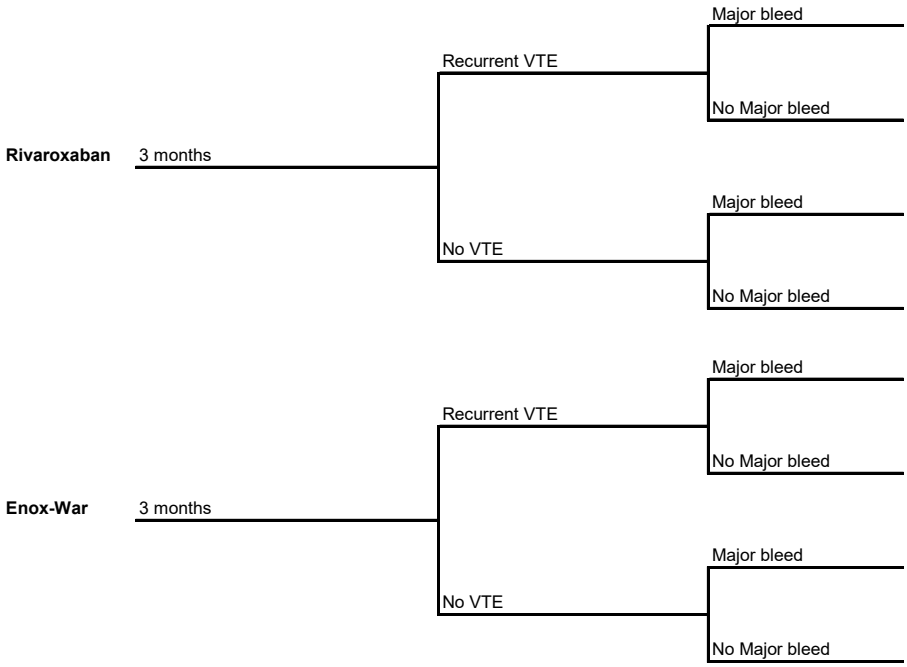

Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin

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 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 hospitalization for a recurrent VTE was taken from a review of the cost of VTE (5) in 18 published studies. The length of stay (LOS) 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 14-24 days. Therefore, a baseline LOS of 6 days was selected with a sensitivity analysis.

The unit costs for in-patient admissions and consultations were taken from the UPFS Tariffs from April 2020. 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/as per quotation received from Bayer (8 July 2020). INR monitoring costs were obtained from the 2020 NHLS Costing Tables.

The medicine costs used in the model are as follows:

Medicine Costs

Medicine	Strength	Dosage form	Pack	Tender or Quotation Price/pack	Tender or Quotation Price /unit	SEP pack size	SEP (+VAT)	SEP (incl VAT)/unit
Rivaroxaban	10 mg	tab	30	R 551.63	R 18.39	30	R 1022.22	R 34.07
Rivaroxaban	15 mg	tab	42	R 772.27	R 18.39	42	R 1428.36	R 34.01
Rivaroxaban	20 mg	tab	28	R 514.85	R 18.39	28	R 952.26	R 34.01
Warfarin	5 mg	tab	100	R 74.19	R 0.74	100	R 227.67	R 2.28
Enoxaparin	40mg	inj	1	R 41.39	R 41.39			

Table 1. Medicine pricing for rivaroxaban, enoxaparin and warfarin

A number of assumptions were made for the model including:

- 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 daily 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 (i.e. only one recurrent VTE regardless of whether in 3, 6, or 12 months).
- Bleeding outcomes of rivaroxaban and standard of care differ (proven by pooled EINSTEIN data).
- All patients were admitted for treatment of recurrent DVT or PE.

4 RESULTS

At a base case pricing of the quoted price from Bayer (8 July 2020) for rivaroxaban (R514.85 per month for 20mg), the incremental cost of treating a patient for 3 months with rivaroxaban would be approximately R211.19. The outcomes of the model were as follows:

	3 months	***6 months***	***12 months***
Rivaroxaban	R 9 836.30	R 12 225.20	R 16 966.21
Enoxaparin-Warfarin	R 9 631.95	R 11 114.35	R 12 352.67
Incremental Cost	R 204.35	R 1 110.85	R 4 613.55

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

If the quotation price of rivaroxaban was reduced by a further 30%, the 3 and 6 month treatment periods would become cost-saving at –R413.46 and R-14.46, 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 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 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 204,35	R 1 110,85	R 4 613,55
Lower (Riv)	1.75%	R 170,40	R 1 075,68	R 4 575,97
Upper (Enox-war)	3.00%	R 117,03	R 1 020,42	R 4 516,91
Event Bleed riv	*1%*	R 204,35	R 1 110,85	R 4 613,55
Lower	0.5%	R 141,77	R 1 048,26	R 4 550,96
No Diff	1.7%	R 291,97	R 1 198,46	R 4 701,16
Upper	2.5%	R 392,10	R 1 298,60	R 4 801,30
Event Bleed enox-war	*1.70%*	R 204,35	R 1 110,85	R 4 613,55
Lower	1.00%	R 291,97	R 1 198,46	R 4 701,16
Upper	3.00%	R 41,64	R 948,13	R 4 450,83
LOS_riv	*5*	R 204,35	R 1 110,85	R 4 613,55
Lower	4	-R 421,65	R 484,85	R 3 987,55
Upper	10	R 3 334,35	R 4 240,85	R 7 743,55
No ICU stay	5	-R 4 279,65	-R 3 373,15	R 129,55
LOS_enox-war	*6*	R 204,35	R 1 110,85	R 4 613,55
Lower	5	R 1 208,75	R 1 736,85	R 5 239,55
Upper	10	-R 2 925,65	-R 2 019,15	R 1 483,55
No ICU stay	5	R 4 688,35	R 5 594,85	R 9 097,55
LOSre	*8*	R 204,35	R 1 110,85	R 4 613,55
Any value	5	R 204,35	R 1 110,85	R 4 613,55
Rivaroxaban (per unit)	18,39	R 204,35	R 1 110,85	R 4 613,55
5% reduction	17,47	R 101,39	R 475,62	R 2 305,70
10% reduction	16,55	-R 1,58	R 735,75	R 3 903,79
15% reduction	15,63	-R 104,55	R 548,20	R 3 548,92
20% reduction	14,71	-R 207,52	R 360,64	R 3 194,04
25% reduction	13,79	-R 310,49	R 173,09	R 2 839,16
30% reduction	12,87	-R 413,46	-R 14,46	R 2 484,28
Major bleed Cost	*5476.00*	*R 2 085.30*	*R 4 233.85*	*R 9 955.70*
Lower	3000	R 249,97	R 1 156,46	R 4 659,16
Upper	15000	R 81,97	R 988,46	R 4 491,16

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 (i.e. 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 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 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 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 772,00		
3 months (20mg daily)	R 1 287,13		R 2 059,40
6 months (20mg daily)	R 2 979,00		R 3 751,05
12 months (20mg daily)	R 6 325,00		R 7 097,57
Enoxaparin+Warfarin		**INR**	
Initial phase (enox 160mg x 8 days)	R 1 324,48		
Initial phase (warfarin 5mg x 26 days)	R 19,29	R 283,80	R 1 627,57
3 months (5mg daily)	R 45,26	R 94,60	R 1 767,43
6 months (5mg daily)	R 113,51	R 236,50	R 1 977,58
12 months (5mg daily)	R 248,54	R 520,30	R 2 396,41

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

The absolute medicine cost difference per patient is R431.83 (3 months), R1 983.62 (6 months) and R5 1119.99 (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 9 836,30	R 9 631,95	R 204,35
6 months	R 12 225,20	R 11 114,35	R 1 110,85
12 months	R 16 966,21	R 12 352,67	R 4 613,55
1000 patients			
3 months	R 9 836 304,09	R 9 631 951,35	R 204 352,74
6 months	R 12 225 199,09	R 11 114 351,15	R 1 110 847,94
12 months	R 16 966 214,09	R 12 352 666,95	R 4 613 547,14
15 000 patients			
3 months	R 147 544 561,29	R 144 479 270,19	R 3 065 291,10
6 months	R 183 377 986,29	R 166 715 267,19	R 16 662 719,10
12 months	R 254 493 211,29	R 185 290 004,19	R 69 203 207,10
25 000 patients			
3 months	R 245 907 602,15	R 240 798 783,66	R 5 108 818,49
6 months	R 305 629 977,15	R 277 858 778,66	R 27 771 198,49
12 months	R 424 155 352,15	R 308 816 673,66	R 115 338 678,49

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 quotation price (provided on 8 July 2020) of rivaroxaban is reduced by 30% 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 quotation price (provided on 8 July 2020) of rivaroxaban (all strengths) is reduced by a further 30%, the incremental cost can be neutralized. A further 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

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Conflicts of interest: None related to rivaroxaban.

Version	Date	Reviewer(s)	Conclusion
First	11 December 2015	Dr J Miot	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 (by 80%), the incremental cost can be neutralized. A price reduction should be negotiated.
Second	10 September 2017	MS TD Leong	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 (by 80%), the incremental cost can be neutralized. A price reduction should be negotiated.
Third	15 July 2020	Ms TD Leong	There is an incremental cost per patient for use of rivaroxaban compared to current standard of care in the treatment and prevention of recurrent VTE, however, if the quotation price (provided on 8 July 2020) of rivaroxaban is reduced by a further 30%, the incremental cost can be neutralized. A further price reduction should be negotiated.

NEMLC RECCOMENDATIONS (Real-time communique July 2020):

- Rivaroxaban (all strengths) may be considered for the indication of treatment and prophylaxis of VTE, provided that the price is reduced sufficiently to achieve cost neutrality with current standard of care. Access should be via a named-patient process as a buy-out during the current pandemic situation.
- The direct oral anticoagulants should be reviewed as a class in the next review cycle. When reviewing the direct oral anticoagulants, availability of a reversal agent, and dosing in the elderly and in renal impairment should also be considered.