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

Initial report: December 2015
Report update: 8 December 2022 (third update)
Medication: Rivaroxaban
Indication: Stroke prevention in atrial fibrillation

1 INTRODUCTION

A motivation was 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 compared to warfarin in the prevention of stroke in patients with non-valvular atrial fibrillation (AF)

The report was updated 25th March 2022 to reflect the updated ICER and BIA based on updated costs (including generic rivaroxaban prices) and population statistics for 2021. At the time there were two generic rivaroxaban formulations available and the cheapest Rivaxored® was selected, however due to the subsequent court action by Bayer, there is now only one generic available, Ixarola® which is the clone of the originator brand Xarelto®.

The model has been revised based on the current Single Exit price of Ixarola®. Other agents currently available on the South African market, include dabigatran and apixaban, which also have clinical evidence for use in AF and other conditions. Rivaroxaban 20mg is a once daily dosing and does not require differential dosing dependent on age. Dabigatran is a twice daily dose and recommends 150mg in patients under 80 years of age, with a 110mg dose of patients over 80 years; and apixaban is dosed 5mg twice a day with dose adjustment to a 2.5mg dose in patients over 80 years, weight under 60 kg and a decreased serum creatinine above 1.5 mg/dL. These formulations are more expensive than the rivaroxaban clone.

2 PHARMACOECONOMICS MODEL - METHODS

A simple markov model was developed. The health states selected for the model were; well (i.e. well with atrial fibrillation), stroke, intracranial haemorrhage, gastrointestinal bleed (major bleed), death. The base case of the model ran for a 10 year time horizon. The age of patients entering the model was 75 years – this was based on the age of entry for the ROCKET trial.

A discount rate of 5% was selected for both cost and clinical inputs.

The only incremental medicine cost was that of the rivaroxaban vs warfarin+INR – i.e. all treatments for atrial fibrillation remained the same.

Only one event could happen to a patient in the duration of the model – for example if they had a stroke in year 2, the model did not allow for a GI bleed in year 3.

A more sophisticated model is probably required to better analyse the concurrent nature of long term consequences, however, it is unclear whether this would materially impact the outcome.

3 CLINICAL INPUTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources. The main effect size variables were taken from the ROCKET-AF trial (Patel MR 2011). These inputs were also used in the published health economic studies and included in the systematic review used in the NEMLC Medicine Review of 26 March 2022.

In order to determine a transition probability (assuming a 1-year cycle period) for the health economics model, an annual event rate is required rather than a total event rate over the duration of the trial. Therefore the event rate per year as reported in the ROCKET trial was used (see table below).

Baseline Event Risk and Relative Treatment Efficacy

All patients were as per the demographics of the ROCKET trial i.e. 75 years or older

Outcome	**Base-case (% per year)**	**Range (CI of HR)**	**P value**
Stroke or Systemic Embolism (ITT)			
Warfarin	2.40%		Combined CHADS2 Scores
Rivaroxaban	2.10%	0.75-1.03	
ROCKET showed p<0.001 for non-inferiority and p=0.12 for superiority			
Using Safety, as-treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.65-0.95	p<0.001 non-inferiority, p=0.02 superiority
Using Per Protocol, as treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.66-0.96	p<0.001 non-inferiority
Intracranial Haemorrhage			
Warfarin	0.70%		
Rivaroxaban	0.50%	0.47-0.93	p=0.02
Major GI Haemorrhage			
Warfarin	2.20%		
Rivaroxaban	3.20%	1.04-1.41	p<0.001
Mortality			
Warfarin	2.20%		
Rivaroxaban	1.90%	0.7-1.02	p=0.07

Table 1. Effect size used in model based on ROCKET trial data

The utilities used to calculate the QALYs were obtained from 2 cost-effectiveness analyses. It was assumed that the utility value applied to the cycle (i.e. 1 year) in which the event occurred. Thereafter the utility returned to that of the Well state (i.e. well with AF).

Health State	***Utilities***
Well with AF	0.98
Ischaemic stroke	0.39
Ischaemic stroke disability	0.75
Post ischaemic stroke no disability	0.95
Haemorrhagic stroke	0.39
Haemorrhagic stroke disability	0.75
Post haemorrhagic stroke no disability	0.95
Major bleed	0.96

Death	0.00

Table 2. Utility values for events and health states

4 COST INPUTS

The medicine costs were based on 2021 data, and the price of warfarin and generic rivaroxaban was obtained from the Single Exit Price database (i.e. a private sector price). The impact of varying the price of rivaroxaban was analysed in the sensitivity analysis.

The total annual medicine cost of treating a patient is shown below;

	per month	**per annum**
Rivaroxaban 20mg	R856.92	R10,283.04
Warfarin	R18.29	R219.42
Warfarin+INR	R74.11	R889.37

Table 3. Annual medicine cost of treating for prevention of stroke

It was assumed that, on average, patients had 12 INRs per annum at a cost of R55.83 per test. In the event of lack of warfarin control, it is likely that patients would have more than 12 INRs in the year and therefore a sensitivity analysis was carried out to assess the impact of up to 36 INRs per annum.

The event costs were adapted from private sector data. These costs need further confirmation as they are currently estimates. Variance in the costs of each event was analyzed in the sensitivity analysis

Event Costs pa	***Rands***
Mortality Cost	1000
Ischaemic Stroke event cost	55000
Post-Ischaemic stroke disability costs	17000
Intracranial Haemorrhagic stroke event cost	55000
Post-Haemorrhagic stroke disability costs	17000
Major bleed disability costs	17000
Major bleed cost	25000
No major bleed cost	360
No disability costs	360

Table 4. Estimated costs per event per annum

5 MODEL RESULTS

The base case incremental cost-effectiveness ratio for the model was **R462 544/QALY.**

		Costs	**Inc Costs**	**QALYs**	**Inc QALYs**	**ICER**
10 yrs	Rivaroxaban	152 281	81 388	6.62	0.18	462 544
	Warfarin	70 893		6.44		
5 yrs	Rivaroxaban	72 060	40 853	3.99	0.06	649 413
	Warfarin	31 206		3.93		
1 yr	Rivaroxaban	12 646	9 256	0.94	0.01	1 756 296
	Warfarin	3 390		0.94		

Table 5. 1-5 year ICERS for Rivaroxaban compared to Warfarin

A sensitivity analysis was carried out to determine which parameters had the most impact on the ICER result. The sensitivity analysis included varying costs, clinical event rates as well as discount rate or time horizon. The Tornado diagram below indicates that the model was most sensitive to a variation in time horizon from 1 to 10 years and stroke event rates. When the benefit of rivaroxaban was increased (i.e. reduced stroke rate), the ICER decreased to R325 935/QALY, when the benefit of warfarin was decreased (increased stroke rate) the ICER also reduced to a similar ICER at R306 385/QALY. When the stroke event rates for warfarin and rivaroxaban were equivalent (i.e. assuming non-inferiority), the ICER increased to above R932 836/QALY. Although the number of INRs did shift the ICER, even at 36 INRs per year, this only dropped the ICER to just above R400 000/QALY. Gastrointestinal bleeds (major) also showed some sensitivity both in utility variation as well as to changes in the event rate of GI bleeds for warfarin.

The model was insensitive to changes in costs or utilities of strokes. Changes in ICH costs and utility also did not have much impact on the sensitivity of the model.

The only parameter which shifted the ICER range in any way below an ICER of R250 000/QALY was the cost of rivaroxaban at a 50% discount.

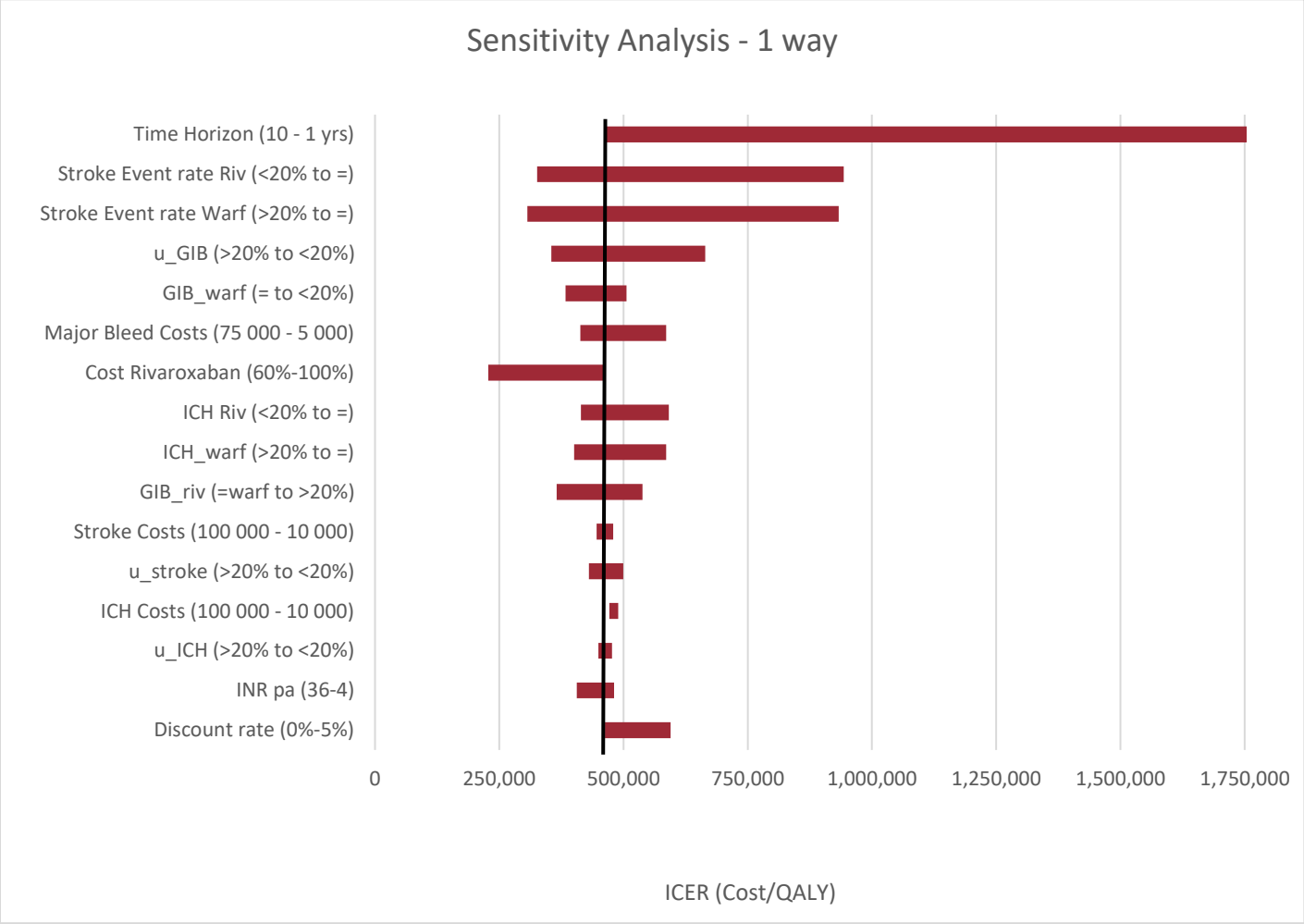

Figure 1. Tornado diagram of one-way Sensitivity Analysis

This model does not take into account multiple simultaneous variations in parameters (i.e. probabilistic sensitivity analysis).

5.1 PUBLISHED COST-EFFECTIVENESS STUDIES

The cost-effectiveness of the DOACs has been carried out in a number of settings and countries. 2 systematic reviews of cost-effectiveness analyses of the DOACs have been published recently (Zheng Y 2014, Ferreira J 2015) as well as a review of the methodologies and results of the DOAC cost-effectiveness studies (Singh SM 2015).

The table below shows the different rivaroxaban studies and the cost-effectiveness model outcomes from these studies

Study	ICER	Setting	Comment
Harrington, 2013	USD 11 150/QALY	USA	Cost effective in 14.9% of simulations
Lee, 2012	USD27 498/QALY	USA	Price of rivaroxaban USD6.8
Kleintjens, 2013	EUR 8 809/QALY	Belgium	Threshold EUR 35 000/QALY
Coyle, 2013	CAD 55 757/QALY	Canada	Cost-effective in 2.1% of simulations
Kansal, 2012	CAD 22 475/QALY	Canada	Threshold CAD 30 000/QALY
Bowrin, 2020	EUR 6 006/QALY	France	Based on real world data for outcomes
Wei, 2021	USD 5 548/QALY	China	Threshold USD 28 443/QALY

Table 6. Summary of published cost-effectiveness outcomes

A meta-analysis of the data up to 2013 by Ferreira et al showed that the mean ICER for rivaroxaban was EUR 17 960±12 005/QALYs which was deemed to be cost effective at a willingness to pay (WTP) threshold of EUR 30 000/QALY.

In the Zheng et al study, a meta-analysis of the data was used to create a new model which showed an ICER of £7203/QALY. At a cost-effectiveness threshold of £20 000/QALY this was considered to be cost-effective. However, this model also showed that dabigatran was more cost-effective than either rivaroxaban or apixaban compared to warfarin and, in fact, was shown to be dominant (i.e. costs less and has better clinical outcomes)

There are a number of uncertainties in the published cost-effectiveness studies and in the analysis carried out here.

The uncertainties related to the clinical trial data include the following;

- Duration of treatment and follow-up; the average duration of follow-up in the trials is around 2 years and therefore the trial-based clinical data is obtained from this information. However, AF is a lifelong condition and therefore treatment is likely to continue on a long-term basis. The clinical outcomes beyond 2 years are uncertain and based on assumption and extrapolations
- Wafarin control (TTR) – generally poorer warfarin control in the public sector in SA than in the trials
- Baseline stroke or haemorrhage risk in SA population
- Age of patients – average age in the trials is around 71-73 years. In SA, the average age of AF patients is similar in the private sector but unclear in the public sector.
- Management of bleeding – treatment patterns and cost

6 THRESHOLD PRICE ANALYSIS

A price threshold analysis was conducted to determine the impact of different prices of rivaroxaban on the ICER. The price of rivaroxaban needed to be discounted by 77.5% to reach an ICER threshold of R100 000/QALY at 10 years and a discount of 90% to reach cost-neutrality.

Price analysis	ICER (R/QALY)
Rivaroxaban 100%	462 544
Rivaroxaban 80%	368 744
Rivaroxaban 70%	321 844
Rivaroxaban 50%	228 044

Table 7. Price impact and threshold analysis of rivaroxaban

7 BUDGET IMPACT ANALYSIS

For the budget impact analysis (BIA), an excel spreadsheet model was developed to take into consideration the following factors; total AF population, patients on warfarin, uptake of rivaroxaban, cost of INR tests, change in effect size of intracranial haemorrhage and major bleeds. The BIA was based on a total population of 50 219 387 million people (Day C 2014). This excluded the approximately 8 million people covered under medical insurance in the private healthcare sector.

The prevalence of AF in males (565/100 000) and females (366/100 000) was derived from the Global AF Study (Chugh et al, 2014). The proportion of patients with non-valvular AF was determined from two studies to give a lower limit of 56% (Stewart et al, 2008 Soweto Heart study) and upper limit of 73% (Jardine et al, 2014). In the Jardine et al AF Survey in South Africa, the proportion of patients on warfarin was around 75%.

	No of Patients
Total AF patients	467 954
AF Males	284 091
AF Females	183 853
Pts with non-valvular AF	262 049
Growth rate in patients with AF	2%
Uptake of rivaroxaban	20% plus 10% pa

Table 8. Estimated prevalence data for non-valvular AF

The costs of treating AF with either warfarin+INR vs rivaroxaban were not inflation adjusted per annum (assuming prices remained static), however a 2% growth rate in the number of AF patients was included. An uptake of 20% in utilization of patients taking rivaroxaban was used for Year 1 in the model and increased by 10% each thereafter. This may vary considerably and it is likely this is an over-estimate in the first year, however may be surpassed in subsequent years once rivaroxaban utilization is established. It is expected that use of rivaroxaban, as with warfarin, is ongoing chronic lifelong treatment. Based on these figures, the incremental budget impact analysis for 2022 (over 5 years) would be approximately R365 million.

Population:	**2022**	**2023**	**2024**	**2025**	**2026**
Pts on Warfarin - total	197 061	201 002	205 022	209 122	213 305
Pts on Warfarin new	157 649	140 701	123 013	104 561	85 322
Pts on Rivaroxaban	39 412	60 301	82 009	104 561	127 983
Costs:					
Cost wafarin+INR - total	668 051 865	681 412 902	695 041 161	708 941 984	723 120 823
Cost wafarin+INR - new	534 441 492	545 130 322	556 032 928	567 153 587	578 496 659
Cost rivaroxaban	498 396 414	508 364 342	518 531 629	528 902 261	539 480 307
Total Cost new	1 032 837 906	1 053 494 664	1 074 564 557	1 096 055 848	1 117 976 965
Incremental cost	**364 786 041**	**372 081 761**	**379 523 397**	**387 113 865**	**394 856 142**

Table 9. Incremental cost-impact analysis of rivaroxaban vs warfarin+INR

8 CONCLUSION

Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, there is still considerable uncertainty around the long-term outcomes and clinical benefits in a mixed population, real-world setting.

In this model, the only variable that could be changed sufficiently to reduce the incremental cost-effectiveness ratio (ICER) to below R250 000/QALY was to reduce the price of the currently available rivaroxaban produce (Ixarola®) by 50% and this is unlikely to be considered cost-effective. A more sophisticated model (with probabilistic sensitivity analysis and more health

states) may have the outcome of further reducing the ICER but at the current model outcome of R462 544/QALY it is unlikely to reduce the ICER to a point which could be considered cost-effective in the public health setting.

Furthermore, the budget impact needs to be considered. The prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be. This will be very dependent on uptake and utilization.

Other factors need to be considered;

- How to define warfarin failure or true warfarin intolerance in order to be eligible for DOACs
- The baseline risk of patients in the current healthcare setting compared to the clinical trial setting
- How to improve warfarin control and monitoring (TTR) as an alternative strategy

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TD Leong (Secretariat to the NEMLC, Essential Drugs Programme, National Department of Health);

Conflicts of interest: JM and TDL have no conflicts of interests related to rivaroxaban.

Version	Date	Reviewer(s)	Conclusion
First	11 December 2015	J Miot	There is an incremental cost per patient for use of rivaroxaban compared to warfarin for the management of atrial fibrillation of R600 000/QALY. Despite a price reduction of rivaroxaban by 80%, the ICER of R600 000/QALY is not cost-effective. Other factors such as affordability, defining warfarin failure/ true warfarin intolerance, baseline risk of patients in clinical setting and how to improve warfarin control and monitoring as an alternative strategy, needs to be considered.
Second	25 January 2022	J Miot, TD Leong	Generic rivaroxaban available at a reduced price was shown not to be cost-effective with a simulated ICER of R188 000/QALY. A reduction in price by 35% (R388/month) reduces the ICER to R100 000/QALY; and a further reduction by 74.5% of the price of generic rivaroxaban (R153/month) results in cost-neutrality with warfarin management. Other factors as described above also needs consideration.
Third	17 November 2022	J Miot	Currently the only generic rivaroxaban that is available (Ixarola®) is the clone at 85% of the SEP of the originator brand. This increases the ICER to R462 544/QALY which is not considered to be cost-effective. Rivaroxaban is currently the cheapest DOAC available on the market.