South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: BBFO

MEDICINE REVIEW

Title: Should DOACs be used for the treatment of DVT or PE in hospitalized adult patients?

Date: 30 November 2021 (original)
Updated: October 2023

Key findings

- We conducted a review of current relevant, high quality practice guidelines and the systematic reviews that informed their recommendations. The American Society of Hematology (ASH) 2020 guideline and National Institute for Health Care Excellence (NICE) 2020 guidelines were reviewed and appraised using AGREE II and found to be of good quality. The systematic reviews that informed the guideline recommendations were appraised using AMSTAR and also found to be of good quality.
- The ASH 2020 guideline is summarized and reported in our review as the recommendations were based on a high quality systematic review of 12 randomised controlled trials, which incorporated all of the 8 clinical trials from Health Technology Assessment that informed the NICE guideline.
- The last search in the ASH guideline was January 2019. Therefore, to ensure we did not miss any new data, we conducted an updated search from 1 February 2019 to 30 September 2021, but we found no new trials.
- The ASH review reported that there is probably no difference in mortality between direct oral anticoagulants (DOACs) and low molecular weight heparin / vitamin K antagonists (LMWH/VKA), RR, 0.99; (95% CI, 0.85-1.15) with moderate-certainty evidence.
- The risk of pulmonary embolism and deep vein thrombosis on LMWH/VKA compared to DOACs were similar (RR, 0.97; 95% CI, 0.77- 1.23) and (RR, 0.80; 95% CI, 0.59-1.09), respectively. The quality of evidence was moderate-certainty evidence.
- The use of DOACs was associated with a reduction in the risk of major bleeding (RR, 0.63; 95% CI, 0.47-0.84; AR ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer); NNH = 167 (95% CI, 112 – 334).
- Overall DOACS have similar mortality and VTE outcomes as LMWH/VKA. However, there is a potential lower risk of major bleeding with DOACs compared to LMWH/VKA.
- Based on the most recent budget impact analysis (refer to Appendix 2 below), there is a cost saving per patient with the use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months following the initial event.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X
Recommendation: Based on this evidence review and the supporting economic analysis, the PHC/Adult Hospital Level Committee recommends rivaroxaban for the treatment of VTE. *Rationale:* There is equivalent efficacy; and probably no difference in mortality between DOACS and vitamin K antagonists (LMWH) in the treatment of venous thromboembolism; (Moderate certainty evidence). DOACS are safer with a lower risk of major bleeding. Rivaroxaban is cheaper at 3 months of therapy. (see Table 2 below) **Level of Evidence: Benefit: Moderate certainty ; Safety: High certainty** **Review indicator:** New evidence of harms, change in price of LMWH; rivaroxaban or other DOACs (dabigatran, apixaban)					
NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC ratified the updated ERC recommendation in support of the use of rivaroxaban for the treatment of VTE as stated above.					
Monitoring and evaluation considerations:					
Research priorities:					

1. Executive Summary

Date: Updated 26 October 2023 (Original review: 06 October 2021)
Medicine (INN): Rivaroxaban, dabigatran, apixaban
Medicine (ATC): Antithrombotic agents (B01A)
Indication (ICD10 code): I80.2
Patient population: Hospitalised acutely ill patients with venous thromboembolism
Prevalence of condition: Prevalence of DVT and PE were estimated between 2.4% - 9.6% and 0.14% to 61.5%, respectively (Danwang C, et al. 2017)
Level of Care: Hospital level care
Prescriber Level: Medical doctor, specialist
Current standard of Care: Low molecular weight heparin / vitamin K antagonists (warfarin)
Efficacy estimates: (preferably NNT) Similar mortality (RR, 0.99; 95% CI, 0.85-1.15) and VTE [(PE: RR, 0.97; 95% CI, 0.77- 1.23); (DVT: RR, 0.80; 95% CI, 0.59-1.09)] outcomes**.**
Motivator/reviewer name(s): Veshni Pillay-Fuentes Lorente, Roland van Rensburg, Tamara Kredo, Nqoba Tsabedze, Marc Blockman, Trudy Leong
PTC affiliation:

2. Name of author(s)/motivator(s)

Veshni Pillay-Fuentes Lorente, Roland van Rensburg, Tamara Kredo, Nqoba Tsabedze, Marc Blockman, Trudy Leong

3. Author affiliation and conflict of interest details

Veshni Pillay-Fuentes Lorente: Stellenbosch University, Tygerberg Hospital; no conflicts of interest to declare.
Roland van Rensburg: Stellenbosch University, Tygerberg Hospital; no conflicts of interest to declare.
Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University; no conflicts of interest to declare.
Nqoba Tsabedze: University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital; declarations include: Servier Laboratories SA (Pty) Ltd - consultancy (To review slide deck on New Hypertension Guideline Management), Novartis SA (Pty)Ltd - Consultancy (To develop a Heart Failure Toolbox. For Management of Acute and Chronic heart failure. Collaboration on a Heart Failure with preserved ejection fraction epidemiological study, Boehringer – Ingelheim, Novonordisk, Eli-Lilly, AstraZeneca, Adcock

Ingram, Pfizer, Merck: Speaker Fees for Webinars & Advisory Board Services, Merck - collaborating on a systematic review of efficacy of Beta Blockers in Black Hypertensives, Wits University – various grants.
Marc Blockman: University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa; declaration - University of Cape Town receives various sponsorships from Pharma Industry.
Trudy Leong: Essential Drugs Programme, National Department of Health; no conflicts of interest – assisted with the costing analyses.

Acknowledgements
- Joy Oliver from the SAMRC for assistance with the updated literature search.
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4. Introduction/ Background

Cardiovascular disease remains amongst the top three causes of death globally.[1] Within the causes of cardiovascular related deaths, venous thromboembolism (VTE) has high mortality rates and commonly presents as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1–3] Hospitalised patients are at higher risk of developing VTE.[3] In Africa, the prevalence of DVT and PE were estimated between 2.4% - 9.6% and 0.14% to 61.5%, respectively.[4] The PE mortality rate ranges between 40% - 69.5%.[4]

The current VTE standard of care treatment constitutes the initiation of low molecular weight heparin (LMWH) plus warfarin followed by the cessation of LMWH once the international normalized ratio (INR) is within the therapeutic range (2.0 – 3.0).[5] Enoxaparin, a LMWH commonly used in South Africa, acts by binding to antithrombin III, the antithrombin III-LMWH complex further inhibits factor Xa. This ultimately leads to the decrease of further fibrin formation and/or expansion.

Warfarin, also known as a vitamin K antagonist, binds and inhibits the enzyme, vitamin K epoxide reductase complex 1 (VKORC1).[6] Vitamin K is required for the synthesis of coagulation factors II (half-life 42 to 72 hours), VII (half-life 4 to 6 hours), IX, and X (half-life 27 to 48 hours), as well as anticoagulants, proteins C and S. These clotting factors are biologically activated by the addition of carboxyl groups to key glutamic acid residues within the proteins' structure. In the process, "active" vitamin K is converted to an "inactive" form, which is then reactivated by VKORC1. The inhibition of VKCOR1 by warfarin causes a depletion of functional vitamin K reserves hence reduces synthesis of active vitamin K dependent clotting factors. The prolonged time taken for depletion of circulating clotting factors and the early depletion of anticoagulants, C and S, predisposes patients to a procoagulant state in the initial phase of warfarin therapy. As a result, parenteral administration of LMWH is required during the initial phase of warfarin therapy until therapeutic INR is achieved. The time taken to reach therapeutic INR is approximately 5 to 6 days.[7]

Direct oral anticoagulants (DOACs) have been on the international market since 2008, with dabigatran being the first to be marketed as a direct thrombin inhibitor. Dabigatran etexilate, a prodrug, is converted to an active metabolite dabigatran which binds to thrombin hence altering the clotting cascade. It has a quick onset of action (approximately 2 hours) and could potentially not require concomitant administration of parenteral LMWH.[8] However, the clinical trials evaluating dabigatran compared to warfarin administered pretreatment with a parenteral anticoagulant to all patients hence currently dabigatran is not recommended as monotherapy.[9] Rivaroxaban was first marketed in 2008, followed by apixaban in 2011. Both drugs are inhibitors of factor Xa and do not require initial administration of parenteral heparin.

DOACs have been considered as an alternate to warfarin in treating VTE as they offer potential important benefits over warfarin such as no INR monitoring, thereby reducing clinic visits, and reduced interindividual patient variability. The initial delayed onset of action of warfarin requires the co-administration of parenteral heparins until therapeutic INRs are

reached, making DOACs an attractive option.[8] Throughout warfarin treatment, regular INR monitoring is required, which leads to many more patient visits. This was initially thought not to be necessary with DOACs. However, the lack of laboratory monitoring of DOACs have been challenged, particularly in special populations such as obesity.[10,11] In pregnancy, DOACs are avoided due to limited evidence to establish efficacy and embryo-fetal safety.[12,13] Many guidelines recommend against the use of DOACs in pregnancy.[14–16]

In South Africa, DOACs have historically been more costly than the current standard of care for VTE, however the price at which rivaroxaban is available in the public sector has been reduced. Due to the perceived benefits; and reduced costs for rivaroxaban, it would be important to evaluate the role of DOACs as an alternate therapy, or as a potentially new standard of care for VTE. This evaluation assessed the clinical benefits and harms as well as costs; in an evidence-based manner, compared to our current standard practice.

5. Purpose/Objective i.e. PICO question:

Should DOACs be used for the treatment of DVT or PE in hospitalized adult patients?

Population – Hospitalised adult patients with DVT or PE
Intervention – DOACs (rivaroxaban, apixaban and dabigatran)
Comparator - LMWH plus VKA (warfarin)
Outcome - Mortality, post-thrombotic limb, embolic events (DVT and PE), recurrent DVT, major bleeds
Study design - A review of clinical practice guidelines with high quality systematic reviews.

6. Methods:

Health Technology Assessments (HTAs): We conducted a search in May 2021 for HTAs on the following electronic databases: The International Network of Agencies for Health Technology Assessment (INAHTA), Epistemonikos and Cochrane library, using a simple search with broad search terms.

Guidelines: A search for current, relevant practice guidelines with available systematic reviews that informed them was conducted on the following websites: National Institute for Health Care Excellence (NICE), American Society of Haematology (ASH), American Heart Association (ACA), Canadian Agency for Drugs and Technologies in Health (CADTH) and the Scottish Medicines Consortium (SMC). Terms included were “DOAC, VTE and VKAs.”

The search and screening of eligible HTAs and guidelines were independently reviewed by two reviewers considering the following factors: most recent, best quality, include most evidence (i.e. relevant trials). All included studies are reported in Table 1: Table of excluded evidence, and the excluded studies are described with reason for exclusion below.

Costing data: we sought costing data from the relevant guidelines, reported under ‘other considerations in the results. We did not appraise the quality of the costing analyses. However, a supporting economic analysis was done – refer to the updated health economics report for rivaroxaban for VTE (Appendix 2),

Critical appraisal: The identified systematic reviews were assessed using the AMSTAR appraisal tool. Related guidelines were appraised using the AGREE II appraisal tool. For the included evidence, we checked the last search dates and then conducted a comprehensive electronic search in two databases (PubMed and CENTRAL) up to 30 September 2021. The search strategy is reported in appendix 1. All identified records were screened by title and abstract for eligibility by a single reviewer on the COVIDENCE software. All eligible studies for full text review were evaluated by two reviewers for full data extraction.

Excluded guidelines and their related systematic reviews:

Table 1. Table of excluded evidence

Author, date	*Type of document*	*Reason for exclusion*
Sterne JAC, et al (2017)[17]	HTA	Search only done up until September 2014. The review authors did not explain their selection of the study designs for inclusion in the review, and did not investigate for publication bias
NICE (originally published 2012, updated 2020)[18]	Guideline (with report of systematic reviews of RCTs)	Included 8 RCTs, all of which were included in the ASH guideline.

7. Evidence synthesis

One HTA was identified but the last search date in the HTA was September 2014. The study was excluded from the review because, 1) the review authors did not explain their selection of the study designs for inclusion in the review, and 2) did not investigate for publication bias. We found two clinical practice guidelines: NICE 2020 guidelines and ASH 2020 guidelines.[18,19] Both guidelines' overall quality of evidence as per AGREE II was rated 6/7. They were downgraded for inadequate reporting on stakeholder involvement. The NICE guideline was excluded since it included 8 RCTs which were all included in the ASH guideline.

The ASH guideline included a systematic review of 12 RCTs and was included in this review. The last search date in the ASH guideline was conducted in January 2019. We conducted an updated search from February 2019 to 30 September 2021 for RCTs. Four-hundred and thirty-eight articles were identified, four articles were duplicate publications, and 420 articles were screened by title and abstract. Fourteen articles were selected for full text review. We identified one potentially eligible trial; however, the full text was not found. The abstract reported that the study included 54 participants with spinal cord injury and results are not likely to affect the outcome effect sizes based on the available systematic review.

Effectiveness of the intervention

1. *Mortality:* The use of a DOAC instead of dose-adjusted VKA (warfarin) to maintain INR between 2.0-3.0 for patients with VTE probably does not impact mortality. The reported risk of mortality is RR, 0.99; 95% CI, 0.85-1.15. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 6 fewer to 6 more). The evidence was assessed as moderate certainty evidence.

2. *Post-thrombotic limb:* This outcome was not reported.

3. *Embolic events (DVT and PE), recurrent DVT:* The risk of PE on DOACs compared to LMWH/VKA were similar (RR, 0.97; 95% CI, 0.77- 1.23; ARR, 1 fewer per 1000 patients; 95% CI, 5 fewer to 5 more. The quality of evidence was moderate certainty. DOACS compared to LMWH/VKA likely results in little or no reduction in the risk of DVT (RR, 0.80; 95% CI, 0.59-1.09; ARR, 5 fewer per 1000 patients; 95% CI, 11 fewer to 2 more). The evidence was assessed as moderate certainty evidence.

4. *Major bleeds:* Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[20] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

   The use of a DOAC was associated with a reduction in the risk of major bleeding (RR, 0.63; 95% CI, 0.47-0.84; ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer) with high certainty evidence.

   In populations with a high risk for bleeding, the use of a DOAC instead of a VKA may lead to a reduction of 8 fewer bleeding events per 1000 patients (95% CI, 11 fewer to 3 fewer; high-certainty evidence). This was based on a risk of

bleeding of 2.1% in patients treated for 6 months (considered high risk population) with LMWH/VKA. Patients treated with LMWH/VKA for 6 months and longer were considered a high risk population group.

Major bleeding in the DOAC group was reported as 1.1% and 1.7% in the LMWH/VKA group. The numbers needed to harm (NNH) associated with major bleeding is 167. In the high-risk population group (2.1% risk of bleeding) the NNH = 100.

Other considerations

We identified five economic analyses reporting the cost comparisons between using DOACs and LMWH/VKA for treatment of VTE. The reports consistently suggest DOAC use is cost-saving compared with warfarin. One report used hypothetical health plan population [21], the other four analyses were informed by real world data.[22–25]

Fifteen economic analyses compared the cost and effectiveness of DOACs versus VKA on the treatment of VTE. All of them suggest DOACs as cost-effective alternative to LMWH or VKA. The studied DOACs mainly include apixaban, and rivaroxaban. A recent systematic review and cost effectiveness analysis found that at a willingness to pay threshold of £20,000–30,000 per QALY in the UK, DOAC are likely cost-effective.[17]
The health economic analysis for rivaroxaban for the treatment of VTE was conducted from a South African national public sector payer perspective and is included in Appendix 2 below. The incremental cost of treating DVT and PE over a period of 3, 6, and 9 months is shown in table 2.

Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 9 months

	0 to 3 months	***0 to 6 months***	***0 to 9months***
Rivaroxaban	*R 10 075*	*R 12 181*	*R 14 214*
Enoxaparin-warfarin	*R 10 739*	*R 11 721*	*R 12 704*
Incremental Cost	*-R 664*	*R 461*	*R 1 510*

Summary of included guideline and related systematic review.

Table 3. Summary of ASH guideline and related systematic review

Author, date	Population	Interventions	Outcomes	Appraisal and comments
Ortel, et al., 2020 American Society of Haematology, 2020 guidelines	Systematic reviews of 12 randomized trials (n = 28 876) Patients with PE or DVT (without cancer)	Initial treatment with LMWH (5-10 days) with dose-adjusted warfarin (INR range, 2.0-3.0) Dabigatran and edoxaban were also administered after an initial treatment of 5 to 10 days with LMWH Rivaroxaban and apixaban were administered without initial parenteral anticoagulants.	Mortality RR, 0.99; 95% CI, 0.85-1.15; ARR, 0 fewer per 1000 patients; 95% CI, 6 fewer to 6 more; moderate certainty evidence Risk of PE RR, 0.97; 95% CI, 0.77-1.23; ARR, 1 fewer per 1000 patients; 95% CI, 5 fewer to 5 more; moderate-certainty evidence Risk of DVT RR, 0.80; 95% CI, 0.59-1.09; ARR, 5 fewer per 1000 patients; 95% CI,	Review: Overall quality of evidence as per AGREE – 6/7 The review search was up to date to January 2019. The review did not include cancer patients. Cost-effectiveness was considered. DOACs was recommended due to cost-effectiveness even though VTE outcomes were not statistically significant. The outcomes were reported as a class effect (DOACs) and in the search strategy all medications within our PICO was incorporated. However, not all the DOACs incorporated in the search strategy is available in South Africa. Recommendation:

		The length of the anticoagulation varied - 3 to 12 months.	11 fewer to 2 more; moderate-certainty evidence), although this was not statistically significant. <u>Risk of major bleeding</u> RR, 0.63; 95% CI, 0.47-0.84; ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer; high-certainty evidence NNH = 167 (DOAC 1.1% and VKA 1.7%) If considering the VKA 2.1%, then NNH = 100 In populations with a high risk for bleeding, the use of a DOAC instead of a VKA may lead to a reduction of 8 fewer bleeding events per 1000 (95% CI, 11 fewer to 3 fewer; high-certainty evidence	For patients with DVT and/or PE, the ASH guideline panel suggests using DOACs over VKAs (conditional recommendation based on moderate certainty in the evidence of effects). The ASH VTE treatment guideline panel has provided a conditional recommendation for the use of DOACs over VKAs as treatment for patients with a new diagnosis of VTE. Although the evidence supporting a reduced risk for bleeding with the use of a DOAC compared with a VKA was of high certainty, the lack of benefit for the VTE outcomes resulted in the conditional recommendation. *Remarks:* This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance < 30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

8. Evidence quality:

The quality of evidence for the outcomes of mortality, pulmonary embolism and deep vein thrombosis was assessed as moderate certainty evidence. Major bleeding was assessed to be of high certainty evidence. The overall quality of the guideline was high and rated 6/7 using the AGREE II tool.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Mortality and VTE outcomes were assessed as moderate certainty evidence.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	Mortality, and VTE outcomes with DOAC and LMWH/VKA use were similar • Mortality: RR 0.99 (0.85 to 1.15) • PE: RR 0.97 (0.77 to 1.23) • DVT: RR 0.80 (0.59 to 1.09)

QUALITY OF EVIDENCE OF HARM

What is the certainty/quality of evidence?

High	Moderate	Low	Very low
X			

High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect

Major bleeding outcomes was assessed as high certainty evidence.

EVIDENCE OF HARMS

What is the size of the effect for harmful outcomes?

Large	Moderate	Small	None

DOACS are safer.

There was a reduction in bleeding risk with DOACs.
<u>*Major bleeding:*</u> RR 0.63 (0.47 to 0.84); 6 fewer per 1,000; (9 fewer to 3 fewer)

Absolute risk reduction = 0.6% and in high-risk population = 1%

(Duration of treatment is 3 to 6 months, but most of the RCTs reviewed in the systematic review were of 3 months duration).

BENEFITS & HARMS

Do the desirable effects outweigh the undesirable harms?

Favours intervention	Favours control	Intervention = Control *or* Uncertain
X		

Mortality and VTE outcomes with DOAC and LMWH/VKA use were similar. There was a reduction of bleeding risk with DOACs.

THERAPEUTIC INTERCHANGE

Therapeutic alternatives available: n/a

This is a therapeutic multiple medicine review.

FEASIBILITY

Is implementation of this recommendation feasible?

Yes	No	Uncertain
X		

DOACs are SAHPRA registered for the treatment of VTE.,
INR monitoring is not required with DOACs.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	X	

Price of medicines/ treatment course

VTE Treatment			
Drug	**Indication: Treatment of DVT & PE**	**Cost for 3 months treatment**	**Cost for 6 months treatment**
Rivaroxaban	15mg BD for D1-D21 then 20mg OD for D22 onwards	1626.74	2945.72
Dabigatran	300 mg taken orally as 150 mg capsules twice daily following treatment with a parenteral anticoagulant for at least 5 days	4267.58	7901.12
Apixiban	10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily	2801.87	5456.27
Warfarin (excludes INR monitoring costs)	Enoxaparin 1mg/kg 12 hourly for 8 days with warfarin 5mg OD	1372.05	1406.67
Assumption 1 month = 30days			
MHPL 1 Sep 2023			
SEP Database 14 Aug 2023			

<table>
<tr>
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<td>NB: Refer to updated health economic analysis for rivaroxaban for treating VTE (March 2023 – See Appendix 2)
<table>
<tr><td></td><td>0 to 3 months</td><td>0 to 6 months</td></tr>
<tr><td>Rivaroxaban</td><td>R 10 075</td><td>R 12 181</td></tr>
<tr><td>Enoxaparin-warfarin</td><td>R 10 739</td><td>R 11 721</td></tr>
<tr><td>Incremental Cost</td><td>-R 664</td><td>R 461</td></tr>
</table>
Other resources:
• Five economic analyses reported the cost comparisons between using DOACs and LMWH/VKA for treatment of VTE. All these reports suggest DOAC use is cost-saving compared with warfarin. Four analyses were based on real world data, whilst the other was a simulated model.
• Fifteen economic analyses compared the cost and effectiveness of DOACs versus VKA on the treatment of VTE. All of them suggest DOACs as cost-effective alternative to LMWH or VKA. The studied DOACs mainly include apixaban, and rivaroxaban.
• A recent systematic review and cost effectiveness analysis found that at willing to pay of £20,000–30,000 per QALY, suggesting that DOAC are likely cost-effective interventions

Given the substantial reduction in price of rivaroxaban and the cost savings in patients treated for up to 3 months, it is recommended that rivaroxaban is included on the EML for the treatment of DVT and PE and the prevention of recurrent VTE.</td>
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<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td>
<td>No included studies, and the Committee was of the opinion that DOACs are acceptable to prescribers.</td>
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<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes [X] No [ ] Uncertain [ ]</td>
<td>Access to INR monitoring is required with warfarin therapy, which is not needed with DOACs.</td>
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Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	30 November 2021	VPL, RvR, TK, NT, MB, TL	DOACs not recommended for the treatment of VTE, as despite no difference in mortality benefit, yet greater reduction in major bleeding of DOACs compared to current standard of care (LMWH+warfarin), DOACs are currently unaffordable.
V6.0	October 2023	MB, ZA	Based on this evidence review and the supporting economic analysis, the PHC/Adult Hospital Level Committee recommends rivaroxaban for the treatment of VTE.

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Appendix 1: Search strategy

Database: **CENTRAL (Issue 9 OF 12, September 2021)**
Date: **30 September 2021**

ID	Search	Hits
#1	[mh "venous thrombosis"] or phlebothrombos*:ti,ab or ("deep vein" next thrombos*):ti,ab or DVT:ti,ab, (Word variations have been searched)	6373
#2	[mh "pulmonary embolism"] or (pulmonary next embolism*):ti,ab or (pulmonary next thrombo*):ti,ab or PE:ti,ab (Word variations have been searched)	7591
#3	[mh "venous thromboembolism"] or (venous next thrombo*):ti,ab or VTE:ti,ab (Word variations have been searched)	6879
#4	#1 or #2 or #3	15555
#5	(oral next anticoagulant*):ti,ab (Word variations have been searched)	2003
#6	[mh dabigatran] or dabigatran:ti,ab'kw or pradaxa:ti,ab,kw or "BIBR 1048":ti,ab,kw (Word variations have been searched)	7591
#7	[mh rivaroxaban] or rivaroxaban:ti,ab,kw or xarelto:ti,ab,kw or "BAY 59 7939":ti,ab,kw or "BAY 597939":ti,ab,kw (Word variations have been searched)	1884
#8	apixaban:ti,ab,kw or eliquis:ti,ab,kw or "BMS 562247":ti,ab,kw or BMS562247:ti,ab,kw (Word variations have been searched)	1027
#9	#5 or #6 or #7 or #8	11019
#10	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees	2026
#11	[mh heparin] or heparin*:ti,ab,kw or liquaemin:ti,ab,kw or UFH:ti,ab,kw or LMW:ti,ab,kw or LMWH:ti,ab,kw or LMWHS:ti,ab,kw or "low-molecular-weight":ti,ab,kw or dalteparin:ti,ab,kw or enoxaparin:ti,ab,kw or nadroparin:ti,ab,kw or tinzaparin:ti,ab,kw or certoparin:ti,ab,kw or parnaparin:ti,ab,kw or ("vitamin K" next antagonist*):ti,ab,kw	15661
#12	#10 or #11	15661
#13	#4 and #9 and #12	804
#14	#4 and #9 and #12 with Publication Year from 2019 to 2021, in Trials	209

Database: **PubMed**
Date: **30 September 2021**

Search	Query	Results
#14	Search: #11 AND #12 Filters: from 2019/1/1 - 2021/9/30 Sort by: Most Recent	553
#13	Search: #11 AND #12 Sort by: Most Recent	2,081
#12	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	4,533,027
#11	Search: #4 AND #9 AND #10 Sort by: Most Recent	3,169
#10	Search: heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMW [tiab] OR LMWH[tiab] OR LMWHS[tiab] OR low-molecular-weight[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab] OR certoparin[tiab] OR parnaparin[tiab] OR vitamin K antagonist*[tiab] Sort by: Most Recent	151,273
#9	Search: #5 OR #6 OR #7 OR #8 Sort by: Most Recent	22,536
#8	Search: apixaban[nm] OR apixaban[tiab] OR eliquis[tiab] OR BMS 562247[tiab] OR BMS562247[tiab] Sort by: Most Recent	4,472
#7	Search: rivaroxaban[mh] OR rivaroxaban[tiab] OR xarelto[tiab] OR BAY 59 7939[tiab] OR BAY 597939[tiab] Sort by: Most Recent	6,858
#6	Search: dabigatran[mh] OR dabigatran[tiab] OR pradaxa[tiab] OR BIBR 1048[tiab] Sort by: Most Recent	5,993
#5	Search: "oral anticoagulant"[tiab] OR "oral anticoagulants"[tiab] Sort by: Most Recent	16,347
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	172,173
#3	Search: Venous thromboembolism[mh] OR venous thrombo*[tiab] OR VTE[tiab] Sort by: Most Recent	55,557
#2	Search: Pulmonary embolism[mh] OR pulmonary embolism*[tiab] OR pulmonary thrombo*[tiab] OR PE[tiab] Sort by: Most Recent	94,223
#1	Search: Venous thrombosis[mh] OR phlebothrombos*[tiab] OR deep vein thrombos*[tiab] OR DVT[tiab] Sort by: Most Recent	68,272

Appendix 2: Budget Impact Analysis (BIA)

National Essential Medicines List Pharmacoeconomics and
Budget impact analysis Update
Adult Hospital Level
Component: BBFO

Date: 25 March 2023 (sixth update)
Medication: Rivaroxaban
Indication: Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thromboembolic events (VTE)

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 decision analysis model was developed in December 2015 to determine the incremental cost for the use of rivaroxaban in the treatment of DVT or PE and the prevention of recurrent VTE compared to standard of care (enoxaparin and warfarin).

The report was reviewed in September 2017 to reflect updated costs, and subsequently updated 8 July 2020, to include a quotation from Bayer of a price 46% lower than SEP. It was further updated to describe costs (including generic Rivaxored® rivaroxaban prices) for 26 November 2021 and then again to describe costs of the clone (Ixarola®) of the originator brand for 17 November 2022 due to a successful patent infringement challenge from Bayer in 2021. Subsequently, Bayer has been awarded a contract based on a substantially reduced price of Xarelto® and the model has been revised to reflect the new pricing available as of January 2023.

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 initial event, 3, 6 and 9 months and therefore no discounting was required.
A decision tree structure was used as per the figure below:

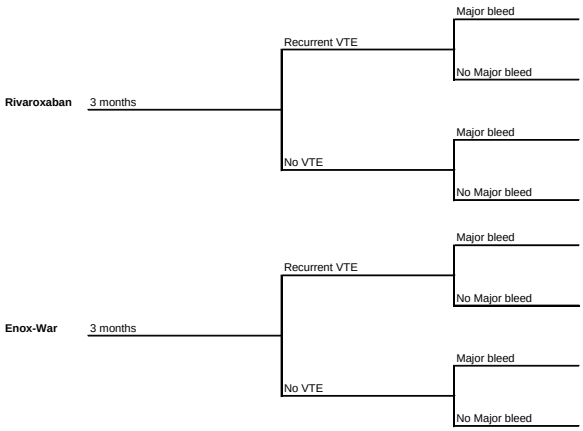

Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin

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 bleed 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 enoxaparin and warfarin (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 for enoxaparin-warfarin and 5 days for rivaroxaban was selected with a sensitivity analysis.

The unit costs for in-patient admissions and consultations were taken from the UPFS Tariffs from April 2022. The medication costs for rivaroxaban and for enoxaparin-warfarin were obtained from the most recent contract database. INR monitoring costs were obtained from the 2021 NHLS Costing Tables and inflation adjusted to 2022.

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	15 mg	tab	42	R 615.52	R 14.66	42		
Rivaroxaban	20 mg	tab	28	R 410.35	R 14.66	28		
Warfarin	5 mg	tab	100	R 60.95	R 0.61	100	R 180.09	R 1.08
Enoxaparin	40mg	inj	1	R 53.61	R 53.61	n/a	n/a	n/a

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 (based on pooled EINSTEIN data).
- Only one further event occurred per time period (i.e. only one recurrent VTE regardless of whether in 3, 6, or 9 months).
- All patients were admitted for treatment of first time or recurrent DVT or PE.

RESULTS

At a base case pricing of the updated price for generic rivaroxaban (R 410.35 for 28 x 20mg tablets), the cost difference of treating a patient from the initial event for up to 3 months with rivaroxaban compared to enoxaparin-warfarin would be a cost saving of approximately R663.87. As the treatment duration increases to 9 months, the incremental cost increases to just over R1500. The outcomes of the model were as follows:

	0 to 3 months	***0 to 6 months***	***0 to 9months***
Rivaroxaban	*R 10 075*	*R 12 181*	*R 14 214*
Enoxaparin-warfarin	*R 10 739*	*R 11 721*	*R 12 704*
Incremental Cost	*-R 664*	*R 461*	*R 1 510*

Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 9 months

The model was most sensitive to changes in length of stay (LOS) and then the price of rivaroxaban (Table 3). If the LOS was further reduced by 1 day for rivaroxaban, the model became cost-saving at 6 months. If patients did not need an ICU stay when on rivaroxaban, the model remained cost-saving even at 6 and 9 months. However, if both rivaroxaban and enox-war had the same LOS (5 days), then the model was no longer cost-saving at 3 months. If the enox-war arm had no ICU stay then the incremental cost increased quite substantially to R6 374 per patient at 9 months. Changing the efficacy event rate or varying the major bleed rate did not impact the model by much. 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**	**9 months**
Event Efficacy (VTE)	*2,10%*	*-R 664*	*R 461*	*R 1 510*
Lower (Riv)	1,75%	-R 701	R 423	R 1 470
Upper (Enox-war)	3,00%	-R 759	R 363	R 1 408
Event Bleed riv	*1%*	*-R 664*	*R 461*	*R 1 510*
Lower	0,5%	-R 728	R 397	R 1 446
No Diff	1,7%	-R 574	R 551	R 1 600
Upper	2,5%	-R 471	R 654	R 1 703
Event Bleed Enox-war	*1,70%*	*-R 664*	*R 461*	*R 1 510*
Lower	1,00%	-R 574	R 551	R 1 600
Upper	3,00%	-R 831	R 294	R 1 343
LOS_Riv	*5*	*-R 664*	*R 461*	*R 1 510*
Lower	4	-R 1 344	-R 219	R 830
Upper	10	R 2 736	R 3 861	R 4 910
No ICU stay	5	-R 5 528	-R 4 403	-R 3 354

LOS_Enox-war	*6*	*-R 664*	*R 461*	*R 1 510*
Lower	5	R 463	R 1 141	R 2 190
Upper	10	-R 4 064	-R 2 939	-R 1 890
No ICU stay	5	R 4 200	R 5 325	R 6 374
Rivaroxaban (per unit)	*14,66*	*-R 664*	*R 461*	*R 1 510*
5% reduction	13,92	-R 746	R 311	R 1 297
10% reduction	13,19	-R 828	R 162	R 1 083
15% reduction	12,46	-R 910	R 12	R 870
20% reduction	11,72	-R 992	-R 137	R 657
25% reduction	10,99	-R 1 074	-R 287	R 444
45% reduction	10,26	-R 1 402	-R 884	-R 409
Enoxaparin price	80mg bd	*-R 252*	*R 872*	*R 1 921*
Major bleed Cost	*6435,35*	*-R 664*	*R 461*	*R 1 510*
Lower	3000	-R 616	R 509	R 1 558
Upper	15000	-R 784	R 341	R 1 390

Table 3. Sensitivity analysis of key parameters for the model at 3, 6, and 9 months

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).

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. A previous economic evaluation conducted by MacQuilkin et al (9) on behalf of the NEMLC in 2019 estimated the number of VTEs in South Africa at 3000 based on procurement data from procurement volumes Contract Circular HP06-2017SVP. Other estimates range from 0.1% of the total population (approx. 60 000 per annum) to around 200 000 patients per annum (10). Additional unknown factors include the ratio of patients only requiring 3 months of treatment compared to longer durations or even lifelong treatment as well as the increased risk of VTE in people living with HIV or TB (10).

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 615		
3 months (20mg daily)	R 1 025		R 1 641
6 months (20mg daily)	R 2 374		R 2 989
9 months (20mg daily)	R 3 649		R 4 264

Enoxaparin+Warfarin	Cost Rx	INR	
Initial phase (enox 160mg x 8 days)	R 1 716		
Initial phase (warfarin 5mg x 26 days)	R 16	R 335	R 2 066
3 months (5mg daily)	R 1 768	R 447	R 2 215
6 months (5mg daily)	R 1 824	R 614	R 2 438
9 months (5mg daily)	R 1 883	R 782	R 2 665

Table 4. Medicine cost of treating DVT and PE for 3, 6, and 9 months

The medicine cost difference per patient is initial phase R-1 116 (cost saving with rivaroxaban), R -127 (3 months), R1 165 (6 months) and R2 381 (9 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 ranging from 500 up to 100 000 with an increasing uptake of rivaroxaban up to 100%, the possible incremental budget impact shifts from being increasingly cost saving for the 3-month treatment duration to an incremental annual cost of around R150 million at 100% uptake for 100 000 patients receiving 9 months of treatment.

3 months incremental budget impact

Incidence	Uptake					Current SOC
Rivaroxaban	20%	40%	60%	80%	100%	*0%*
Enox-War+INR	80%	60%	40%	20%	0%	*100%*
500	-66 387	-132 775	-199 162	-265 550	-331 937	*5 369 585*
1500	-199 162	-398 325	-597 487	-796 649	-995 812	*16 108 754*
3000	-398 325	-796 649	-1 194 974	-1 593 299	-1 991 623	*32 217 509*
10000	-1 327 749	-2 655 498	-3 983 247	-5 310 996	-6 638 745	*107 391 695*
60000	-7 966 494	-15 932 987	-23 899 481	-31 865 974	-39 832 468	*644 350 173*
100000	-13 277 489	-26 554 978	-39 832 468	-53 109 957	-66 387 446	*1 073 916 955*

9 months incremental budget impact

Incidence	Uptake					Current SOC
Rivaroxaban	20%	40%	60%	80%	100%	*0%*
Enox-War+INR	80%	60%	40%	20%	0%	*100%*
500	150 988	301 975	452 963	603 951	754 939	*6 352 238*
1500	452 963	905 926	1 358 890	1 811 853	2 264 816	*19 056 715*
3000	905 926	1 811 853	2 717 779	3 623 706	4 529 632	*38 113 430*
10000	3 019 755	6 039 510	9 059 265	12 079 020	15 098 775	*127 044 765*
60000	18 118 530	36 237 059	54 355 589	72 474 118	90 592 648	*762 268 593*
100000	30 197 549	60 395 099	90 592 648	120 790 197	150 987 747	*1 270 447 655*

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

Assuming a likelihood of around 60% uptake in 10 000 patients per year the incremental savings for 3 months would be in the region of R4 million at 3 months and shifting to just over R9 million at 9 months. However, if an assumption is made that the proportion of patients requiring only 3 months of treatment is 70% and those needing 9 months of treatment is 30% then the incremental impact is a saving of R46 996 pa. If that ratio shifts to 50% 3 months and 50% 9 months then the annual budget impact is R1 692 006.

Incremental cost	2023	2024	2025	2026	2027
Uptake of 10 000pts	60%	60%	60%	60%	60%
70% (3m), 30% (9m)	-46 996	-49 815	-52 804	-55 972	-59 331

50% (3m), 50% (9m)	1 692 006	1 793 526	1 901 138	2 015 206	2 136 119

Table 6. Budget impact at varying proportions of patients requiring 3m and 9m treatment

RECOMMENDATION

There is a cost saving per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months following the initial event, however, as the length of treatment increases then the cost difference increases to an additional cost of up to R1 510 per patient for 9 months of treatment.

The initial budget impact shows a cost saving at 3 months however, the increase in budget could be considerable depending on the number of eligible patients, rate of uptake and proportion of patients requiring short-term compared to longer-term treatment. A more sophisticated model is required to determine the impact of varying more than one parameter at a time. A follow-up study in South Africa should be 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. The impact on quality of life of the patient who no longer needs to take warfarin and have regular INR monitoring has not been determined.

Given the substantial reduction in price of rivaroxaban and the cost savings in patients treated for up to 3 months, it is recommended that rivaroxaban is included on the EML for the treatment of DVT and PE and the prevention of recurrent VTE.

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.

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Model (2015) developed by: Dr J Miot
Affiliation: Health Economics and Epidemiology Research Office (HE²RO), University of Witwatersrand

Report updated by: TD Leong
Affiliation: 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 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	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	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.
Fourth	25 November 2021	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 SEP of generic rivaroxaban (Rivaxored®) is reduced by a further 25%, the incremental cost can be neutralized. A further price reduction should be negotiated.
Fifth	17 November 2022	J Miot	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 SEP of generic rivaroxaban (Ixarola®) is reduced by a further 45%, the incremental cost can be neutralized. A further price reduction should be negotiated.
Sixth	25 March 2023	J Miot	There is a cost saving per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months however, the cost difference increases to an additional cost of up to R1 510 per patient for 9 months of treatment.