Technology Guidance

Non-vitamin K antagonist oral anti-coagulation agents (NOACs)

for the treatment and secondary prevention of venous thromboembolism

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Rivaroxaban 15 mg and 20 mg tablets, and apixaban 2.5 mg and 5 mg tablets for adults to:
  - treat deep vein thrombosis (DVT) and pulmonary embolism (PE); and
  - prevent recurrent DVT and PE; and

Subsidy status

Rivaroxaban 15 mg and 20 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications.

MAF assistance **do not** apply to:

- the use of rivaroxaban for isolated distal DVT; or
- rivaroxaban 2.5 mg and 10 mg tablets.

Apixaban 2.5 mg and 5 mg tablets are recommended for reclassification from MAF to the MOH Standard Drug List (SDL).

SDL subsidy or MAF assistance **do not** apply to any strengths of dabigatran.

Updated: 1 Jul 2022

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of non-vitamin K antagonist oral anti-coagulation agents (NOACs; apixaban, rivaroxaban and dabigatran) for treating venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) and preventing recurrent DVT and PE in adults in August 2017. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence was considered in line with the registered indications for each NOAC agent.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

1.4. Manufacturers of apixaban and dabigatran, which were not recommended for subsidy at the August 2017 meeting due to unacceptable cost effectiveness or budget impact, were invited to submit revised price proposals, which the Committee considered in April 2018. The manufacturer of dabigatran did not submit a revised proposal.

1.5. Manufacturers of apixaban and rivaroxaban, which were listed on the MAF, were invited to submit price proposals for their products to be reclassified to SDL, which the Committee considered in November 2021. As part of the exercise, a pricing proposal was also sought for rivaroxaban 10 mg, a newly registered strength indicated for preventing recurrent DVT and PE.

Clinical need

2.1. In August 2017, the Committee noted that in local clinical practice, patients with proximal DVT, PE, or symptomatic distal DVT typically received anticoagulant treatment, unless contraindicated. The main first-line agents used were low molecular weight heparin (LMWH) plus warfarin, and NOACs, with about half of all patients with VTE receiving NOACs. Local experts estimated that about 1 in 5 patients who initiated

treatment with warfarin switched to NOAC therapy because of compliance difficulties with repeated blood taking required with warfarin use, or because of labile international normalised ratio.

2.2. In August 2021, the Committee noted that there had been a significant increase in prescribing and use of NOACs in the public healthcare institutions since rivaroxaban and apixaban were subsidised in 2018.

Clinical effectiveness and safety

3.1. In 2017, the Committee agreed that enoxaparin with warfarin, and warfarin alone were the appropriate comparators to the NOACs for treatment and secondary prevention indications respectively.

3.2. Pivotal trials considered for treating VTE included EINSTEIN-DVT and EINSTEIN-PE for rivaroxaban, RE-COVER and RE-COVER-II for dabigatran, and AMPLIFY for apixaban. Results of the studies showed all NOACs were non-inferior to warfarin for lowering risk of symptomatic recurrent VTE.

3.3. The Committee understood only patients who had symptomatic PE, or proximal DVT were recruited in these trials; patients with isolated distal DVT were not included. The Committee agreed that the use of NOACs in patients with isolated distal DVT was not well-supported by clinical evidence.

3.4. Both dabigatran and apixaban were shown to result in a significantly lower risk of major bleeding as well as combined major or clinically relevant non-major bleeding in the overall population, while rivaroxaban was associated with a significantly lower risk of major bleeding only in the PE population.

3.5. For the secondary prevention of VTE, the Committee noted that only dabigatran had been studied in a population at high risk of recurrent VTE compared with an active control. Based on the RE-MEDY trial, dabigatran was shown to be non-inferior to warfarin for time-to-first symptomatic, recurrent VTE. It also resulted in a significantly lower rate of major or clinically relevant non-major bleeding compared with warfarin. Rivaroxaban and apixaban, were only studied in placebo-controlled trials, which did not recruit patients with high risk of recurrent VTE (EINSTEIN-EXT and AMPLIFY-EXT). All three NOACs were shown to be superior to placebo for risk of symptomatic, recurrent VTE, and the Committee acknowledged that they were likely to result in similar or more favourable efficacy outcomes when studied in high-risk patients.

Cost effectiveness

4.1. In 2017, the Committee considered the cost effectiveness of NOACs based on

published studies, and noted no local economic evaluations were available. The Committee acknowledged that results from overseas published economic evaluations in the UK setting showed both apixaban and rivaroxaban were cost-effective treatment options (ICER £20,000-£30,000/QALY gained) compared with warfarin for treating VTE. All three NOACs were also considered to be cost-effective treatment options (less than £35,000/QALY gained) when used for secondary prevention in patients who were at high risk of recurrent fatal VTE and low bleeding risk. The Committee concluded that at the prices proposed by the manufacturers, NOACs were likely to be cost effective compared with warfarin in Singapore.

4.2. Given all three NOACs were considered to be comparable in effectiveness and safety, the Committee concluded at the August 2017 meeting that rivaroxaban, which had the lowest cost, was the most cost-effective option based on a cost-minimisation approach.

4.3. In April 2018, following a revised price proposal for apixaban, the Committee agreed that the cost of apixaban was reasonable and could be considered an acceptable use of healthcare resources. Dabigatran remained at a higher cost compared with rivaroxaban and apixaban and was the least cost-effective option.

4.4. In November 2021, following price proposals from the manufacturers for apixaban and rivaroxaban to be reclassified from MAF to SDL, the Committee noted that apixaban was the most cost-effective NOAC based on a cost-minimisation approach. The Committee also noted that the proposed price of rivaroxaban 10 mg was higher than 20 mg on a per mg basis, but was of the view that a linear pricing structure would be preferred.

Estimated annual technology cost

5.1. In April 2018, the Committee estimated around 850 people with VTE in Singapore would benefit from government assistance for rivaroxaban and apixaban. The annual cost impact was estimated to be less than SG$500,000 at the prices proposed by the manufacturers. In November 2021, the Committee considered that the annual cost impact could increase following reclassification of apixaban to SDL.

Recommendations

6.1. Based on the evidence presented in August 2017, the Committee recommended rivaroxaban 15 mg and 20 mg tablets be listed on the MAF for treating DVT and PE, and preventing recurrent DVT and PE in adults, given its acceptable clinical and cost effectiveness, and a high clinical need for this treatment.

6.2. In April 2018, the Committee also recommended apixaban 2.5 mg and 5 mg tablets be listed on the MAF in line with the same clinical criteria as rivaroxaban, following an acceptable price reduction offered by the manufacturer.

6.3. In November 2021, the Committee recommended apixaban 2.5 mg and 5 mg tablets be reclassified from MAF to SDL. At the price proposed by the manufacturer, the Committee recommended rivaroxaban 15 mg and 20 mg tablets be retained on the MAF in line with the existing clinical criteria.

VERSION HISTORY

Guidance on non-vitamin K antagonist oral anti-coagulation agents (NOACs)
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This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1.	**Publication of guidance (rivaroxaban listed on MAF)**	
	Date of Publication	5 Feb 2018
2.	**Guidance updated to extend MAF listing to apixaban**	
	Date of Publication	1 Oct 2018
3.	**Guidance updated to reclassify apixaban from MAF to SDL**	
	Date of Publication	1 Jul 2022

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 18 August 2017, 26 April 2018, 18 August 2021 and 9 November 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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Chief HTA Officer
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg