Novel oral anticoagulants for non-atrial fibrillation indications: utilisation analysis

Drug utilisation sub-committee (DUSC)

October 2014

Abstract

Purpose

To the examine utilisation of medicines referred to as the novel oral anticoagulants (NOACs), rivaroxaban, apixaban and dabigatran for the treatment of deep vein thrombosis (DVT), the prevention of venous thromboembolism (VTE), treatment of pulmonary embolism (PE) and for the prevention of recurrent venous thromboembolism.

To compare the predicted versus actual utilisation of rivaroxaban for acute symptomatic DVT and PE.

Data Source / methodology

Data for the number of prescriptions for rivaroxaban, dabigatran and apixaban were extracted from the Department of Human Services (DHS) Medicare Pharmacy Claims database for the period August 2009 to March 2014, inclusive. The number of patients treated for DVT and PE was determined by counting the number of individual de-identified personal identification numbers in the specified time period. The use of rivaroxaban for DVT and PE is compared to the use predicted in the submission.

Key Findings

- The DUSC considered that the use of NOACs for the prevention of VTE in hip and knee replacements has remained quite low and stable since it was reviewed in June 2011, as expected for a short term treatment for a limited patient group.

- The DUSC considered that the use of rivaroxaban for treatment of DVT and PE, and prevention of recurrent VTE is steadily increasing.

- In the most recent 12 months of data (April 2013 to March 2014) there were 1,587 prescriptions dispensed for apixaban, 2,279 for dabigatran and 115,179 for rivaroxaban.

These values exclude use for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF).

- Of the 115,179 prescriptions dispensed for rivaroxaban, 70 % of these were for treatment of DVT or prevention of recurrent VTE.
- In its first year of listing for DVT, 12,646 patients were supplied rivaroxaban for DVT treatment or prevention of recurrent VTE.
- Rivaroxaban was listed for pulmonary embolism for eight months of the 12 month period April 2013 to March 2014. Of the 115,179 prescriptions dispensed for rivaroxaban, 11 % of these were for pulmonary embolism.

- As predicted in the March 2012 DUSC advice, the number of patients, prescriptions and cost were underestimated in the rivaroxaban submission for confirmed acute symptomatic DVT without symptomatic PE, and for the prevention of recurrent venous thromboembolism. In year 1, the number of patients supplied with rivaroxaban for DVT and prevention of recurrent VTEs (including item codes 2160Q and 2268J) was 7.01 times higher than predicted, the number of prescriptions 4.07 times higher than predicted, and the benefits paid 8.42 times higher than predicted.

Purpose of analysis

To the examine utilisation of medicines referred to as the novel oral anticoagulants (NOACs), rivaroxaban, apixaban and dabigatran for the treatment of deep vein thrombosis (DVT), the prevention of venous thromboembolism (VTE), treatment of pulmonary embolism (PE) and for the prevention of recurrent venous thromboembolism.

To compare the predicted versus actual utilisation of rivaroxaban for acute symptomatic DVT and PE.

Background

Pharmacology

Rivaroxaban and apixaban are selective inhibitors of the coagulation Factor Xa.[1,2]

Dabigatran is a competitive and reversible direct thrombin inhibitor. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.[3]

Therapeutic Goods Administration (TGA) approved indications

Rivaroxaban is TGA registered for:

- Prevention of venous thromboembolism in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks).
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.
- Treatment of DVT and PE and for the prevention of recurrent DVT and PE.

Apixaban is TGA registered for:

- Prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery.
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

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[1] Xarelto (rivaroxaban). Australian Approved Product Information. Sydney: Bayer Australia Ltd. Approved 24 November 2008, most recent amendment 15 January 2015. Available from <www.ebs.tga.gov.au>.
[2] Eliquis (apixaban). Australian Approved Product Information. Sydney: Pfizer Australia Pty Ltd. Approved 21 July 2011, most recent amendment 16 June 2014. Available from <www.ebs.tga.gov.au>.
[3] Pradaxa (dabigatran). Australian Approved Product Information. Sydney: Boehringer Ingelheim Pty Limited. Approved 24 November 2008, most recent amendment 20 June 2014. Available from <www.ebs.tga.gov.au>.

Dabigatran is TGA registered for:

- Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

Dosage and administration

Table 1 outlines the indications and associated recommended dosage[1,2,3] for apixaban, dabigatran and rivaroxaban.

Table 1: Indications and dosage of rivaroxaban, apixaban and dabigatran

Brand name and sponsor	Indication	Dose and frequency of administration
Rivaroxaban (Xarelto®), Bayer Australia Ltd	VTE Prevention in total hip replacement	A 10 mg tablet taken once daily. The initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established. Treatment duration of 5 weeks is recommended.
	VTE Prevention in total knee replacement	A 10 mg tablet taken once daily. The initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established. Treatment duration of 2 weeks is recommended.
	Treatment of DVT and PE and prevention of recurrent DVT and PE	Initial treatment of acute DVT and PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and the prevention of recurrent DVT and PE. During the initial 3 weeks of acute treatment 15 mg should be taken twice daily. After the initial 3 weeks treatment should be continued at 20 mg once daily. Therapy should be continued as long as the VTE risk persists.
Apixaban (Eliquis®) Bristol-Myers Squibb Australia Pty Ltd	VTE Prevention in total hip replacement	The recommended dose is 2.5 mg taken twice daily. The initial dose should be taken 12 to 24 hours after surgery. In patients undergoing hip replacement surgery, the recommended duration of treatment is 32 to 38 days.
	VTE Prevention in total knee replacement	The recommended dose is 2.5 mg taken twice daily. The initial dose should be taken 12 to 24 hours after surgery. In patients undergoing knee replacement surgery, the recommended duration of treatment is 10 to 14 days.
Dabigatran (Pradaxa®) Boehringer Ingelheim Pty Ltd	VTE Prevention in total hip replacement	The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg. For patients with moderate renal impairment the

Brand name and sponsor	Indication	Dose and frequency of administration
		recommended dose is 150 mg once daily, taken as 2 capsules of 75 mg. Treatment should be initiated orally within 1–4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily. Treatment duration of 28–35 days is recommended.
	VTE Prevention in total knee replacement	The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg. For patients with moderate renal impairment the recommended dose is 150 mg once daily, taken as 2 capsules of 75 mg. Treatment should be initiated orally within 1–4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily. Treatment duration of 10 days is recommended.

Source: rivaroxaban, apixaban and dabigatran Product Information[Error! Bookmark not defined.,Error! Bookmark not fined.,Error! Bookmark not defined.]

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

Clinical situation

DVT and PE are two aspects of one disease process known as venous thromboembolism (VTE). In DVT, a thrombus (blood clot) forms in the deep veins of the leg or pelvis where it may cause pain, tenderness and swelling of the leg. In PE, some or all of the thrombus becomes detached and moves from the vein through the right side of the heart to lodge in one or more pulmonary arteries. PE may cause shortness of breath, bloody sputum, chest pain, faintness and heart failure. Massive PE leads to death.[4]

[4] National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: National Health and Medical Research Council; 2009. Available from <http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/guideline_prevention_venous_thromboembolism.pdf>.

PBS listing details (as at 1 July 2014)

The details of the PBS listings of rivaroxaban, dabigatran and apixaban are shown in Table 2.

Table 2: PBS listing of rivaroxaban, dabigatran and apixaban

Item	Name, form & strength, pack size	Maximum quantity	Repeats	DPMQ	Brand name and manufacturer
2160Q	RIVAROXABAN rivaroxaban 15 mg tablet, 42	1	0	$138.89	Xarelto® Bayer Australia Ltd
2268J*	RIVAROXABAN rivaroxaban 20 mg tablet, 28	1	5	$94.85	
9465E	RIVAROXABAN rivaroxaban 10 mg tablet, 10	1	1	$39.65	
9466F	RIVAROXABAN rivaroxaban 10 mg tablet, 15	1	1	$54.16	
9467G	RIVAROXABAN rivaroxaban 10 mg tablet, 30	1	0	$101.14	
9468H	RIVAROXABAN rivaroxaban 10 mg tablet, 30	1	0	$39.65	
9469J	RIVAROXABAN rivaroxaban 10 mg tablet, 15	1	0	$54.16	
9318K	DABIGATRAN dabigatran etexilate 75 mg capsule, 10	2	1	$45.88	Pradaxa® Boehringer Ingelheim Pty Ltd
9319L	DABIGATRAN dabigatran etexilate 110 mg capsule, 10	2	1	$37.94	
9320M	DABIGATRAN dabigatran etexilate 75 mg capsule, 60	1	0	$121.01	
9321N	DABIGATRAN dabigatran etexilate 110 mg capsule, 60	1	0	$96.25	
9322P	DABIGATRAN dabigatran etexilate 75 mg capsule, 10	2	0	$45.88	

9323Q	DABIGATRAN dabigatran etexilate 110 mg capsule, 10	2	0	$37.94	
Item	**Name, form & strength, pack size**	**Max. quant.**	**Repeats**	**DPMQ**	**Brand name and manufacturer**
5054B	APIXABAN apixaban 2.5 mg tablet, 30	1	0	$54.34	Eliquis® Bristol-Myers Squibb Australia Pty Ltd
5061J	APIXABAN apixaban 2.5 mg tablet, 60	1	0	$101.54	
5500L	APIXABAN apixaban 2.5 mg tablet, 20	1	0	$39.79	

*Note that rivaroxaban item code 2268J includes use for atrial fibrillation.
Source: pbs.gov.au.

Restriction

All NOACs are PBS listed as Authority Required (streamlined) benefits.

Rivaroxaban is PBS listed for:

- Confirmed acute symptomatic deep vein thrombosis in patients that must not have symptomatic pulmonary embolism;
- Confirmed acute symptomatic pulmonary embolism;
- Prevention of recurrent venous thromboembolism in patients that have a history of venous thromboembolism;
- Prevention of venous thromboembolism in patients undergoing total knee replacement;
- Prevention of venous thromboembolism in patients undergoing total hip replacement; and
- Prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (outside the scope of this analysis).

Dabigatran is PBS listed for:

- Prevention of venous thromboembolism in patients undergoing total knee replacement;
- Prevention of venous thromboembolism in patients undergoing total hip replacement; and
- Prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (outside the scope of this analysis).

Apixaban is PBS listed for:

- Prevention of venous thromboembolism in patients undergoing total knee replacement;

- Prevention of venous thromboembolism in patients undergoing total hip replacement; and
- Prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (outside the scope of this analysis).

Date of listing on PBS and changes to listing

Table 3 outlines the dates apixaban, dabigatran and rivaroxaban were listed on the PBS and changes to their PBS listings.

Table 3: PBS listing dates and changes to listings for NOACs

Drug	Indication	Date
Rivaroxaban	Listed for prevention of VTE in hip replacements	1 August 2009
Rivaroxaban	Listed for prevention of VTE in knee replacements	1 August 2009
Dabigatran etexilate	Listed for prevention of VTE in hip replacements	1 April 2010
Dabigatran etexilate	Listed for prevention of VTE in knee replacements	1 April 2010
Apixaban	Listed for prevention of VTE in hip replacements	1 January 2012
Apixaban	Listed for prevention of VTE in knee replacements	1 January 2012
Rivaroxaban, dabigatran and apixaban	Restrictions changed to specify whether patient requires 10, 15 or 30 days of treatment and if this is required to complete a course of therapy	1 July 2012
Rivaroxaban	Listed for acute symptomatic deep vein thrombosis	1 December 2012
Rivaroxaban	Listed for prevention of recurrent venous thromboembolism. Patient must not have symptomatic pulmonary embolism.	1 December 2012
Rivaroxaban	Listed for pulmonary embolism	1 August 2013
Rivaroxaban	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (out of scope for this analysis)	1 August 2013
Apixaban	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (out of scope for this analysis)	1 September 2013
Dabigatran etexilate	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (out of scope for this analysis)	1 September 2013
Rivaroxaban, dabigatran and apixaban	Rivaroxaban, dabigatran and apixaban for prevention of VTE in patients undergoing total hip or knee replacements changed from an Authority Required listing to an Authority Required (STREAMLINED) listing	1 January 2014

Current PBS listing details are available from the PBS website.

Relevant aspects of the PBAC consideration

Rivaroxaban

Prevention of VTE in hip and knee replacements

The PBAC (March 2009) recommended listing of rivaroxaban tablet 10 mg for the prevention of venous thromboembolism in adult patients undergoing elective total replacement of the hip or knee on the basis of uncertain but overall acceptable cost-effectiveness compared with enoxaparin. The submission claimed that rivaroxaban was superior in terms of comparative effectiveness and equivalent in terms of comparative safety over enoxaparin for prevention of VTE in patients undergoing elective total hip replacement and elective total knee replacement.

The PBAC concluded that oral rivaroxaban 10 mg once daily was more effective, but possibly less safe, than subcutaneous enoxaparin 40 mg once daily in the restrictions requested for PBS listing and across the range of durations of use of enoxaparin currently used in Australia. The Committee recommended listing on the basis of uncertain but overall acceptable cost-effectiveness.

The submission estimated the likely number of patients/year expected to receive rivaroxaban for total hip and knee replacement would be between 50,000 and 100,000 in Year 5, with a financial cost/year to the PBS of less than $10 million.

The submission's estimates however were considered an approximation due to uncertainty regarding the expected rate of uptake of rivaroxaban and the current level of use of enoxaparin for this indication.

For further details refer to the Public Summary Document from the March 2009 PBAC meeting.

Treatment of confirmed acute symptomatic DVT without symptomatic pulmonary embolism and prevention of recurrent VTE

At its March 2012 meeting, the PBAC recommended listing rivaroxaban 15 mg and 20 mg tablets on the PBS on a cost minimisation basis compared with enoxaparin and warfarin with a cost offset for the additional INR tests associated with warfarin treatment.

The submission estimated the likely number of patients treated per year to be less than 10,000 patients in year 5 of listing, at an estimated net cost per year to the PBS of less than $10 million in year 5.

The PBAC considered that the estimates may have been underestimates, with the main areas of uncertainty being the incidence rates used in the submission, market uptake, duration of therapy and usage outside the requested PBS restriction (such as primary prophylaxis for DVT and/or use beyond 2 years).

For further details refer to the Public Summary Document from the March 2012 PBAC meeting.

Treatment of acute symptomatic PE and prevention of recurrent VTE

At its March 2013 meeting the PBAC recommended rivaroxaban's Authority Required (streamlined) listing be extended to include treatment of acute symptomatic pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE), on a cost minimisation basis compared with enoxaparin 80 mg twice daily followed by INR adjusted warfarin, at same treatment cost for enoxaparin 80mg twice daily followed by INR adjusted warfarin.

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

The PBAC considered there was potential for usage beyond the requested restriction, particularly in patients with PE who are haemodynamically unstable or with chronic thromboembolic disease. It accepted that these patients groups were likely to be small and recommended that the restriction not be confined to the trial population.

The PBAC was concerned that current prescribing software packages and listings of item numbers generated different listings with different costs. Practically, this may result in wrong indications being chosen and drug costs may increase as a consequence of selecting the wrong streamlined code. The PBAC suggested that DUSC may wish to monitor usage and this information be used to inform consideration as to how to manage total cost. The PBAC considered the greatest uncertainty in usage is the number of patients that may switch from warfarin to rivaroxaban.

For further details refer to the Public Summary Document from the March 2013 PBAC meeting.

Dabigatran

Prevention of VTE in adult patients undergoing total hip replacement (THR) surgery

At its March 2009 meeting, the PBAC deferred its consideration of dabigatran as an Authority Required benefit for the prevention of venous thromboembolic events in adult patients undergoing elective total hip replacement in order to give the applicant an opportunity to compare dabigatran with rivaroxaban, another new oral therapy available for the same patient population.

The comparator nominated in the submission was enoxaparin 40 mg given 12 hours preoperatively and then once daily for 30 days post-surgery.

Although the PBAC accepted that subcutaneous enoxaparin injection was an appropriate main comparator at the time the submission was lodged, the PBAC considered that oral rivaroxaban tablet was a more appropriate comparator given that it is also a new oral

therapy for the prevention of VTE in patients undergoing elective total replacement of the hip (or knee).

The submission presented a cost minimisation analysis on the basis that dabigatran 220 mg and dabigatran 150 mg were equi-effective to enoxaparin 40 mg.

For further details refer to the Public Summary Document from the March 2009 PBAC meeting.

Prevention of VTE in adult patients undergoing total hip replacement (THR) and total knee replacement (TKR)

The submission to the November 2009 PBAC meeting presented a cost-minimisation analysis, based on the implicit assumption that both dabigatran 220 mg and dabigatran 150 mg are equi-effective to rivaroxaban 10 mg.

The PBAC considered there was insufficient evidence provided to support this assumption. Only drug costs were included in the economic analysis. Neither costs associated with prophylaxis failure (VTEs), nor costs of treating adverse events, were included.

The PBAC accepted the cost analysis provided in the March 2009 submission, a cost-minimisation analysis on the basis that dabigatran 220 mg and dabigatran 150 mg were equi-effective to enoxaparin 40 mg, was reasonable (see also March 2009 Public Summary Document).

The PBAC recommended the Authority Required PBS listing of dabigatran for prevention of venous thromboembolic events in adult patients undergoing total hip replacement (THR) and total knee replacement (TKR) on a cost minimisation basis compared with enoxaparin. The equi-effective doses are dabigatran 220 mg is equivalent to enoxaparin 40 mg.

The PBAC agreed that the results of the indirect comparison of dabigatran and rivaroxaban are uncertain and conclusions from these analyses cannot be used for the purposes of comparing these drugs. Further, the PBAC did not accept the submission's claim that dabigatran is no worse than rivaroxaban. Although a head-to-head trial of dabigatran and rivaroxaban would be required to provide a definitive comparison, the PBAC considered that in all likelihood dabigatran is less efficacious than rivaroxaban, but noted that it is also less expensive.

The PBAC expressed concerns about the comparison of 150 mg dabigatran versus 40 mg enoxaparin. The PBAC stated the relative risk of 1.28 and the 95 % confidence interval (0.93, 1.78) for the primary outcome does not support the claim of non-inferiority based on the PBAC's view of the non-inferiority margin of 4 % absolute risk difference noting that this margin was not the study non-inferiority margin.

The likely number of patients per year expected to receive dabigatran was estimated to be in the range of 10,000 to 50,000 in Year 5.

The financial savings per year to the PBS were estimated to be less than $10 million in Year 5. The submission's estimate was considered uncertain due to difficulties in assessing the likely uptake of dabigatran, given the current and future use of enoxaparin and rivaroxaban for this indication are unknown.

For further details refer to the Public Summary Document from the November 2009 PBAC meeting.

Apixaban

Prevention of VTE in patients undergoing total knee replacement (TKR) or total hip replacement (THR)

At its July 2011 meeting the PBAC recommended the listing of apixaban on a cost minimisation basis compared with rivaroxaban. The requested restriction was accepted as consistent with both rivaroxaban and dabigatran, the oral anti-thrombotic agents listed at the time for this patient group.

The PBAC accepted rivaroxaban as the appropriate comparator, in preference to dabigatran, and enoxaparin was accepted as a secondary comparator. An indirect comparison of the primary efficacy endpoint demonstrated that apixaban is statistically non-inferior to rivaroxaban in total knee replacements. The PBAC noted there may be some limitations with regards to the exchangeability of the trials, but this was insufficient to alter the PBAC's acceptance of the clinical claim of non-inferiority.

A similar conclusion was drawn with respect to the indirect comparison of the primary efficacy endpoint with respect to non-inferiority between apixaban and rivaroxaban in total hip replacements. With respect to safety, the PBAC noted that the overall trend was that the incidence of bleeding events numerically favoured apixaban over enoxaparin. This was not the case with rivaroxaban. Although there are limitations with respect to exchangeability of the trials, on the basis of the indirect comparison the PBAC accepted that apixaban is likely to be no worse than rivaroxaban in terms of bleeding.

The likely number of patients was estimated in the submission to be between 10,000 and 50,000 in Year 5, with an estimated net cost to the PBS of less than $10 million in Year 5, using the original requested maximum quantity of 20 tablets for TKR.

In its pre-PBAC response, the Sponsor advised that a 30 tablet pack would be available which was claimed to result in the listing being cost neutral to the PBS.

For further details refer to the Public Summary Document from the July 2011 PBAC meeting.

Approach taken to estimate utilisation and reviews by DUSC

Prevention of VTE in hip and knee replacements

The submission to the March 2009 PBAC meeting for rivaroxaban for VTE prophylaxis in patients undergoing total hip and total knee replacements was examined by DUSC at its February 2009 meeting. The DUSC considered the potential for use beyond the population specified by the restriction was high. The proportions of THR and TKR patients that currently received thromboprophylaxis with enoxaparin, the average duration of current prophylaxis, and therefore the current number of prescriptions for this indication per year were considered to be uncertain.

The utilisation of rivaroxaban and dabigatran for the prevention of VTE in patients undergoing total hip and total knee replacements was examined by DUSC at its June 2011 meeting. The DUSC found that the submission's estimate of the number of prescriptions was a substantial overestimate and that the concern that rivaroxaban is associated with bleeding into the joints appears to be a factor in limiting use. The DUSC could only review PBS-listed use of enoxaparin, however this use did not appear to have been reduced since the inclusion of rivaroxaban on the PBS.

The DUSC requested that the DUSC Secretariat review anticoagulant products pre and post the release of the new NHMRC guidelines for VTE prophylaxis to determine if these guidelines resulted in a change in clinical practice.

Treatment of confirmed acute symptomatic DVT without symptomatic pulmonary embolism and prevention of recurrent VTE

The March 2012 PBAC submission for rivaroxaban for the treatment of confirmed acute symptomatic DVT without symptomatic PE, and the prevention of recurrent VTE used a mixed epidemiological and market share approach to estimate use. The sponsor commissioned a treatment survey of 150 physicians which was used to determine current usage of DVT treatment, duration of treatment, percentage of patients with proximal versus distal DVT, and the expected uptake of rivaroxaban in this setting. The DUSC considered the methodologies adopted in the market research to be unreliable; the response rate was not reported, it was considered likely the sample was not representative and the qualitative research presented did not include rivaroxaban's safety profile. The DUSC considered the market uptake assumptions to be an underestimate given the perceived advantages of rivaroxaban compared to warfarin. The DUSC noted the estimated prescriptions included only 12 months of rivaroxaban therapy despite the requested restriction including a potential of two years duration of therapy, and considered the estimates of treated patients were likely to be significantly higher than predicted in the submission.

Treatment of acute symptomatic pulmonary embolism (PE) and prevention of recurrent VTE

The March 2013 PBAC submission for rivaroxaban for PE used a mixed epidemiological and market share approach. The incidence estimate was derived from AIHW data. The PBAC observed that the estimated number of patients treated with rivaroxaban may be

underestimated as a consequence of patients switching from existing warfarin therapy to rivaroxaban, and the potential for leakage beyond the requested restriction. The submission was not considered by the DUSC.

Methods

Data for the number of prescriptions for rivaroxaban, dabigatran and apixaban were extracted from the Department of Human Services (DHS) Medicare Pharmacy Claims database for the period August 2009 to March 2014, inclusive. The use of rivaroxaban for DVT and PE is compared to the use predicted in the submission.

Data were extracted based on the date that the prescription was supplied to the patient. The number of patients treated was determined by counting the number of individual de-identified personal identification numbers in the specified time period. New (initiating) patients were defined as those with no prior PBS or RPBS prescription of the drug for the indication since it was listed for acute symptomatic DVT and prevention of recurrent VTE in December 2012, as determined by the streamlined code. Data manipulation was undertaken using SAS.

Unique patients were counted for rivaroxaban by calendar year and the prescribed indication (using streamlined code to determine indication). PBS item codes specifically for prevention of VTE in hip and knee replacements and prevention of stroke in patients with AF were not included in this analysis.

Expenditure data for rivaroxaban for DVT, for the first and partial second year of listing, and rivaroxaban for PE, from the time of listing (August 2013) to the most recent data available (March 2014), are presented by indication as determined by the streamlined code.

DUSC (June 2014) requested an analysis by state, given that differing hospital preferences may impact which NOACs are supplied in the community. As the analysis focused on indications for which rivaroxaban is the only PBS listed NOAC, it was determined that an analysis by state would not be informative.

An analysis of duration of treatment was considered for DVT and PE treatment, as the duration of treatment was estimated in the submission to be 12 months, but could be up to two years, and the PBS restriction does not specify length of treatment. There were not sufficient data available to complete this analysis. The earliest this analysis could be presented is the February 2016 DUSC meeting.

Limitations of the data

Utilisation of NOACs for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF) is out of scope of this review. Rivaroxaban has item codes specifically for patients with AF, however AF is also one of four indications listed under PBS item code 2268J. The indications listed under this PBS item code are acute symptomatic deep vein thrombosis, prevention of recurrent venous thromboembolism, acute symptomatic pulmonary embolism and AF. Although each indication has a separate

streamlined code, in the most recent 12 months of data this field is blank against 9 % of prescriptions when AF is included, and 15 % of prescriptions when AF is excluded.

Apixaban and dabigatran have separate item codes for AF. There is some small use of the AF streamlined code for dabigatran and apixaban against PBS item codes for prevention of VTE in hip and knee replacements. This suggests miscoding of indications in the data.

Results

Analysis of drug utilisation

Overall utilisation

The number of prescriptions supplied for apixaban, dabigatran and rivaroxaban by month is shown in Figure 1 and totals for the twelve months to March 2014 are shown in Table 4. AF is excluded.

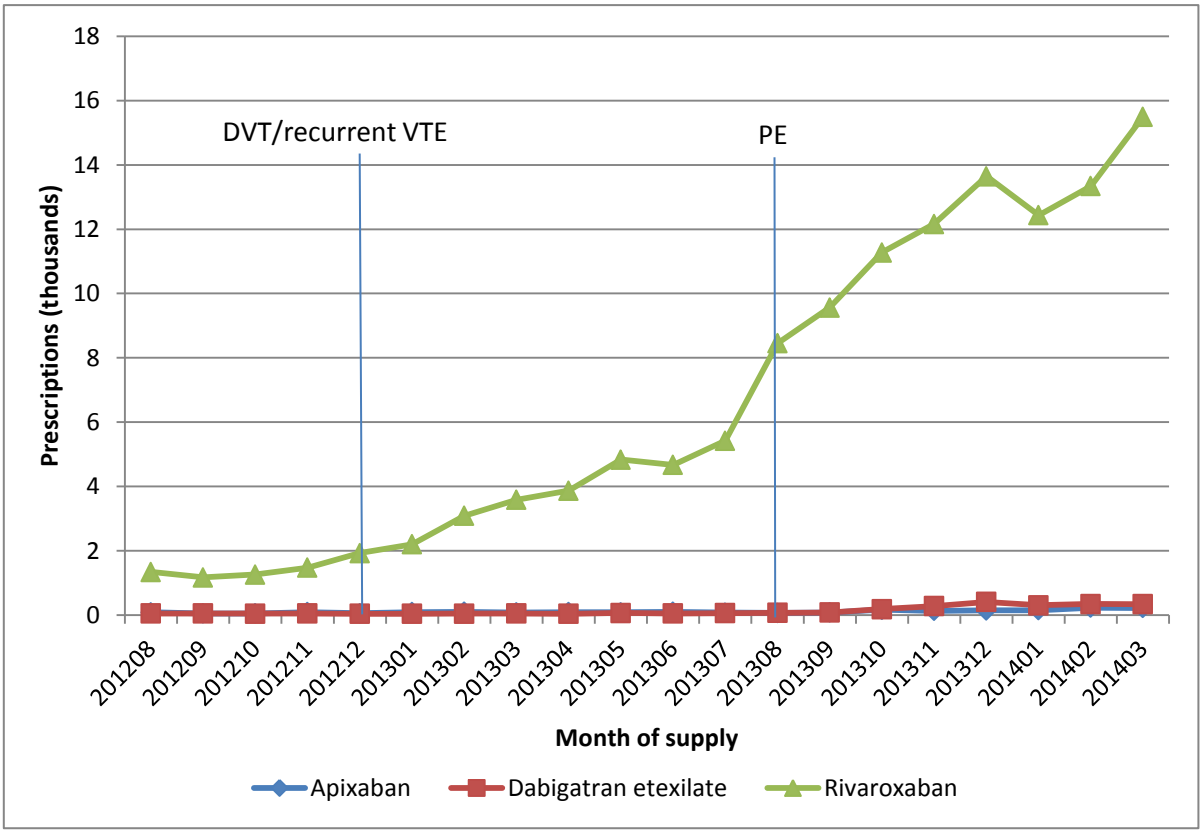

Figure 1: NOAC prescriptions supplied by drug without the streamlined code for AF included, from August 2012.

Rivaroxaban was listed 1 December 2012 for DVT and prevention of recurrent VTE and 1 August 2013 for PE.

Table 4: Number of prescriptions for apixaban, dabigatran and rivaroxaban for the most recent 12 months of available data (April 2013 to March 2014), excluding AF

Drug name	Apixaban	Dabigatran etexilate	Rivaroxaban
Number of prescriptions	1,587	2,279	115,179

The analysis of use of NOACs for indications other than non-valvular atrial fibrillation shows rivaroxaban dominates the market (Figure 1). Other than non-valvular atrial fibrillation, dabigatran and apixaban are only listed for the prevention of VTE in hip and knee replacements. In addition to the prevention of VTE in hip and knee replacements, rivaroxaban is also listed for acute symptomatic DVT, prevention of recurrent VTE, and for PE.

The use of rivaroxaban for VTE prophylaxis in hip and knee replacements is possibly higher than dabigatran and apixaban because it was the first NOAC listed for these indications. Rivaroxaban was listed for this indication eight months before dabigatran and more than two years before apixaban. It is likely the relatively low use of apixaban is mainly due to its late entry to the market.

Use of dabigatran and apixaban for VTE prophylaxis in hip and knee replacement is low and stable; relative to the trend for rivaroxaban, as additional indications have been PBS listed. Therefore the remainder of this analysis will focus on rivaroxaban use in non-AF indications.

The DUSC considered that the use of NOACs for the prevention of VTE in hip and knee replacements has remained quite low and stable since it was reviewed in June 2011, as expected for a short term treatment for a limited patient group.

Rivaroxaban

The number of prescriptions supplied for rivaroxaban by indication, excluding AF, is shown in Figure 2.

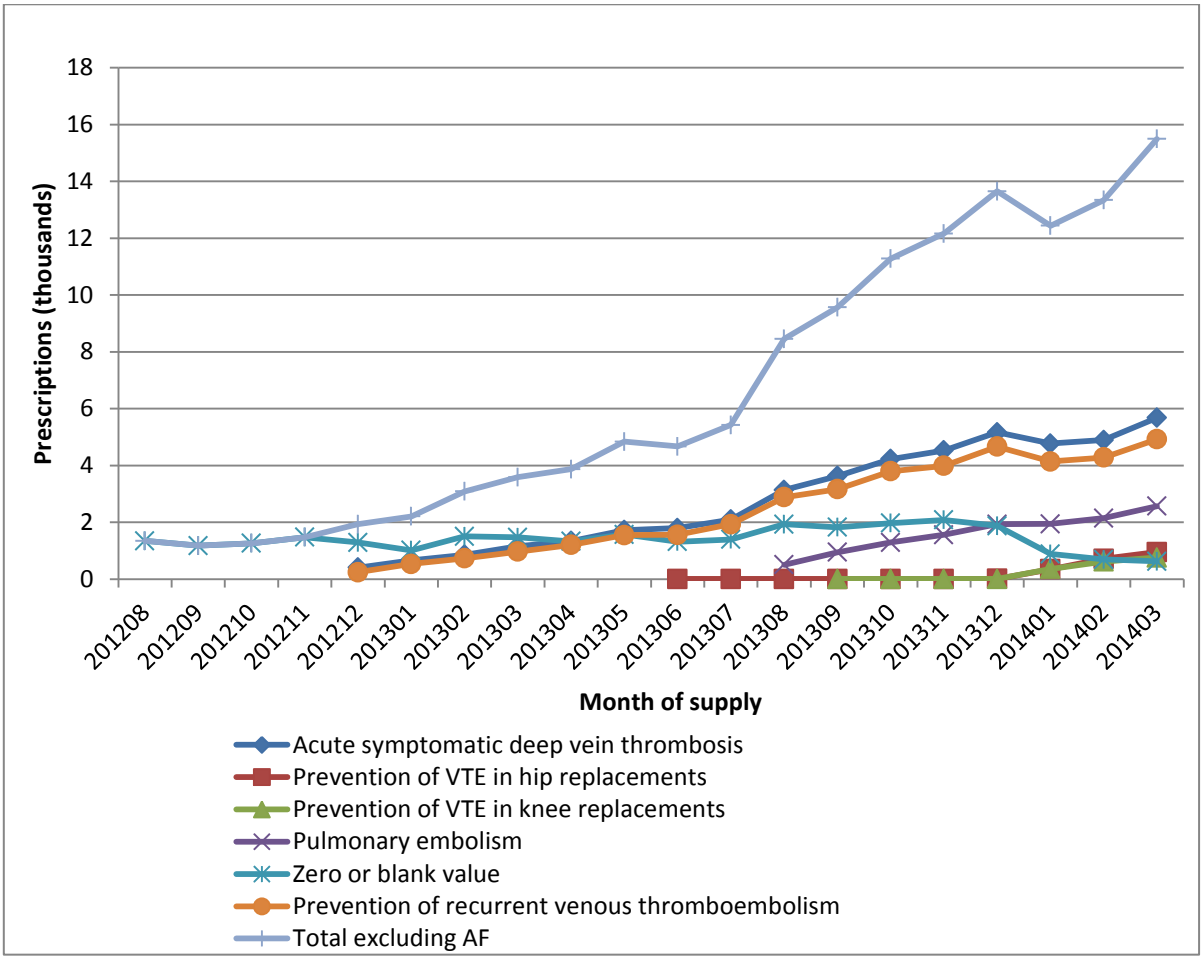

Figure 2: Prescriptions supplied for rivaroxaban by indication (using streamlined code to determine indication) from June 2012.

PBS item codes for prevention of VTE in hip and knee replacements are included. PBS item codes and streamlined codes for AF are not included.

Prior to the listing of rivaroxaban for DVT in December 2012, rivaroxaban was PBS listed for prevention of VTE in hip and knee replacements. The listing for prevention of VTE in hip and knee replacements was an Authority Required listing until it was streamlined on 1 January 2014. Until January 2014 nearly all the use of rivaroxaban for prevention of VTE in hip and knee replacements is represented by zero or blank values, as these prescriptions were approved through the prior approval authority system (usually via telephone).

Since 1 January 2014, all rivaroxaban indications have been listed as Authority Required (STREAMLINED). However, in the three months since 1 January 2014, a small number of rivaroxaban prescriptions are missing the streamlined code. While blank streamlined codes often represent cases where a telephone authority for increased quantities or repeats has been sought, every PBS listing for rivaroxaban has a note stating no increase in the maximum quantity or number of units may be authorised and no increase in the maximum number of repeats may be authorised. It is possible that in transitioning from telephone to streamlined authority, some prescribers have continued to phone for authority; these

prescriptions would appear in the data with a blank streamlined code. It is likely that the number of blank codes will decrease as prescribers become familiar with the change.

Generally the use of rivaroxaban for prevention of VTE in hip and knee replacements is relatively low and stable. Use of rivaroxaban did begin to increase in December of 2012, due to the listing of acute symptomatic DVT and recurrent VTE, and then increased further from August 2013 when it was listed for pulmonary embolism. Use of rivaroxaban for treatment of DVT, PE and prevention of VTE, is steadily increasing, as can be seen in Figure 2.

Table 5 shows the number of prescriptions for rivaroxaban for indications other than AF for the twelve months to March 2014.

Table 5: Number of prescriptions and percentage of total for rivaroxaban for the most recent 12 months of available data (April 2013 to March 2014), excluding AF

Acute symptomatic deep vein thrombosis	Prevention of recurrent venous thromboembolism	Prevention of VTE in hip replacements	Prevention of VTE in knee replacements	Pulmonary embolism	Zero or blank value	Total
42,977	38,063	2,036	1,743	12,878	17,482	115,179
37%	33%	2%	2%	11%	15%	100%

Rivaroxaban was listed for pulmonary embolism from 1 August 2013.

Table 6 lists the patient numbers for rivaroxaban from 2012. Rivaroxaban was listed for acute symptomatic DVT and prevention of recurrent VTE on 1 December 2012. Only PBS item codes 2160Q and 2268J are included (i.e. item codes for prevention of VTE in hip and knee replacements are excluded). However, PBS item code 2268J includes a listing for prevention of stroke or systemic embolism in patients with AF. This is not inclusive of all AF patients, just those supplied item 2268J.

Table 6: Patient numbers for rivaroxaban by year and indication (using streamlined code)

	2012		2013		2014	
	All patients by indication	Initiating patients by indication	All patients by indication	Initiating patients by indication	All patients by indication	Initiating patients by indication
Acute symptomatic deep vein thrombosis	294	294	8,175	7,946	6,600	2,849
Prevention of recurrent venous thromboembolism	197	197	4,805	4,596	4,880	901
Pulmonary embolism			2,120	2,120	2,710	1,229
AF			20,384	20,383	24,142	6,972
Blank or zero value	123	123	1,256	1,167	647	222

The included PBS item codes are 2160Q and 2268J. Initiating patients are defined by no prior prescription for these item codes since listing on 1 December 2012. Note that if a patient receives rivaroxaban under more than one streamlined code in a given year, that patient is only counted once, for the streamlined code of their first prescription in that year.

Rivaroxaban was listed for pulmonary embolism from 1 August 2013.

Analysis of expenditure

The expenditure on rivaroxaban in the first two years of listing for acute symptomatic DVT, prevention of recurrent VTE and PE are shown in Tables 7 and 8. A Special Pricing Arrangement applies to rivaroxaban and hence the expenditure shown in the tables below, which is based on the published price of rivaroxaban, is indicative of trends only.

Table 7: Expenditure for rivaroxaban for acute symptomatic DVT and prevention of recurrent venous thromboembolism

	Acute symptomatic deep vein thrombosis	**Prevention of recurrent venous thromboembolism**	**Total DVT**
Year 1	$2.1 M	$1.8 M	$3.9 M
Year 2 (partial)*	$1.7 M	$1.4 M	$3.1 M

*Year 2 of DVT includes December 2013 to March 2014

The expenditure is based on the published price for rivaroxaban, not the actual price, as a Special Pricing Arrangement Applies.

Table 8: Expenditure for rivaroxaban for pulmonary embolism

	Pulmonary embolism
Year 1 (partial)*	$1.1 M

*Year 1 of PE includes August 2013 to March 2014

The expenditure is based on the published price for rivaroxaban, not the actual price, as a Special Pricing Arrangement Applies.

The values in Tables 7 and 8 are based on date of supply. There may be small differences between these values and publicly available Medicare Australia date of processing data.

Analysis of actual versus predicted utilisation

The comparison of predicted and actual use of rivaroxaban for DVT includes item codes 2160Q and 2268J. Prescriptions supplied under the streamlined code for AF, PE or with blank or zero values have been excluded.

A comparison of the predicted and actual number of patients, number of prescriptions and cost of rivaroxaban in the first two years of listing for the treatment of DVT and the prevention of recurrent VTE is presented in Table 9.

Table 9: Comparison of predicted and actual prescriptions and cost to the Commonwealth for rivaroxaban for DVT in the first two years of listing

	Patients			Prescriptions			Benefit		
	Predicted	Actual	Number of times higher the actual is than the predicted	Predicted	Actual	Number of times higher the actual is than the predicted	Predicted (millions)	Actual (millions)	Number of times higher the actual is than the predicted
Year 1	1,804	12,646	7.01	11,822	48,063	4.07	$0.5	$3.9	8.42
Year 2	3,862	6,252	1.62	29,850	38,513	1.29	$1.2	$3.1	2.59

*Year 1 is from 1 December 2012 to 30 November 2013, Year 2 is from 1 December 2013 to 30 April 2014 (5 months of data)

Note that the counts of patients, prescriptions and benefit for rivaroxaban includes acute symptomatic DVT and prevention of recurrent venous thromboembolism.

The predicted values in Table 9 above are from the estimates of utilisation agreed between the Sponsors and the Department prior to listing. For each patient, the streamlined code associated with their first prescription during each 12 month period since listing was used to determine the indication. If a patient was supplied prescriptions during the time period for two streamlined codes, this analysis counted the patient once, against the first streamlined code they were prescribed. Prescriptions supplied with a streamlined code for AF, PE or with blank or zero values were excluded from the data set prior to counting the patients. Prescriptions for VTE prophylaxis in hip and knee replacements are not included as these indications have separate item codes.

In the first year of listing (December 2012 to November 2013) the number of patients supplied with rivaroxaban for DVT or prevention of recurrent VTE was 7.01 times higher than predicted, the number of prescriptions 4.07 times higher than predicted, and the benefits paid 8.42 times higher than predicted.

In the first year of listing the actual number of patients of 12,646 included;

- 3,983 for acute symptomatic deep vein thrombosis (initial treatment);
- 3,947 for acute symptomatic deep vein thrombosis (continuing treatment); and
- 4,716 for prevention of recurrent venous thromboembolism.

The number of patients who received their first prescription of rivaroxaban in the first year of listing for prevention of recurrent venous thromboembolism was higher than the number who received their first prescription for initial treatment of acute symptomatic DVT. The group receiving rivaroxaban for prevention of recurrent venous thromboembolism likely includes patients who have a history of VTE (including DVT or PE), who may have switched from other anticoagulant therapies, such as warfarin and enoxaparin.

The number of patients who received their first prescription of rivaroxaban in the first year of listing for continuing treatment of acute symptomatic deep vein thrombosis was almost as high as the number who received their first prescription for initial treatment. The Australian Medicines Handbook recommends rivaroxaban for treatment of DVT as 15 mg twice daily for three weeks, then 20 mg once daily.[5] It is possible treatment of these patients was initiated in hospital, and the first PBS rivaroxaban prescription they were supplied was for continuing treatment after discharge.

Overall the number of patients, prescriptions and cost were underestimated by the submission, as predicted in the March 2012 DUSC Advice. Possible reasons that the use was underestimated are:

- The incidence was underestimated. The DUSC commented (in the advice to the March 2012 PBAC meeting) that the estimated incidence rate (0.0504 %) was an underestimate. The DVT incidence rates used in the submission were based on a meta-analysis by Fowkes et al (2003), which did not include patients with recurrent DVT and did include many older studies that may not have reflected the aging population. A comparison of hospital admissions of people with DVT (extracted using case-mix data by AR-DRG, F63A and F63B) and the 53 % rate of admission to hospital in EINSTEIN implied that DVT incidence was 50 % higher than assumed in the submission.

- The market uptake, including patients switching from other treatments, was higher than estimated by the submission. The DUSC (March 2012 advice) stated the market uptake assumptions used in the submission are a likely underestimate given the perceived advantages of rivaroxaban compared to warfarin (does not require regular INR testing) and being a first in class oral therapy.

- The duration of use is higher than expected. The DUSC (March 2012 advice) stated the estimate of the number of rivaroxaban packs supplied is dependent upon duration of use; and the estimated prescriptions included only 12 months of rivaroxaban therapy despite the requested restriction including a potential of two

[5] Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2013.

years of therapy. The final PBS listing did not specify a maximum duration of therapy. There were not sufficient data available to complete a duration of treatment analysis for the current report. The DUSC noted that a meaningful analysis of duration of treatment will not be possible until there is at least two years of date of supply data available for these indications.

- Some use of rivaroxaban may be outside of the PBS restriction, for example, in post-surgical prophylaxis other than total hip and knee replacements. The DUSC (March 2012 advice) considered there was potential for use outside the requested listing for prophylaxis in other indications where an oral dose form may be preferred by patients.

- Incorrect selection of streamlined codes by the prescriber or incorrect entry by the pharmacist. Item 2268J includes multiple streamlined authority indications, including DVT and AF. Given that the AF market is much larger than the DVT market even a small amount of miscoding of AF as DVT could account for the much higher apparent use of rivaroxaban.

The DUSC considered the utilisation for treatment of PE and DVT, and prevention of recurrent VTE, may include some use in AF if miscoded using the streamlined code.

DUSC actions

The DUSC requested an analysis of duration of treatment, noting that the earliest this analysis could be presented to give meaningful results is the February 2016 DUSC meeting.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Bayer Australia Ltd: Bayer will work with the Department in order to update the previous estimates regarding the predicted versus actual patient numbers associated with rivaroxaban utilisation in Australian clinical practise. Bayer will bring forward the matter to the PBAC for consideration and hopes this comprehensive data analysis brought forward by the DUSC is considered in the appropriate context.

Boehringer Ingelheim Pty Ltd: The sponsor has no comment.

Bristol-Myers Squibb Australia Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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