Apixaban (Eliquis) for stroke prevention in non-valvular atrial fibrillation (a-PIX-a-ban)

KEY POINTS

Apixaban is an oral anticoagulant with a twice-daily dosing regimen
It inhibits factor Xa and is PBS listed for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) who meet certain criteria.

Apixaban reduced the incidence of stroke and systemic embolism in people with NVAF
In trials, patients taking apixaban had fewer haemorrhagic strokes and a lower incidence of major bleeding compared with those on warfarin.

Long-term safety and efficacy data are not available
The key clinical trial had a median follow-up of 1.8 years.

There is no antidote for apixaban
Advise patients to seek medical attention for unexplained bruising, blood in urine or black stools.

Apixaban may be an alternative to warfarin for some patients
Patients unable to maintain stable INR for reasons other than adherence, or unable to tolerate warfarin or undergo INR monitoring, may benefit from apixaban.

PBS listing

Authority required (Streamlined)
Prevention of stroke or systemic embolism.
Apixaban is PBS listed for the prevention of stroke or systemic embolism in patients with NVAF who also have one or more of the following risk factors:

- prior stroke (ischaemic or unknown), transient ischaemic attack or systemic embolism (non-central nervous system)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- heart failure and/or left ventricular ejection fraction ≤ 35%.

What is it?
Apixaban is an orally active selective inhibitor of factor Xa. It has a direct mechanism of action and does not require the presence of antithrombin. Factor Xa is an essential element of the coagulation cascade, promoting conversion of prothrombin to thrombin. Apixaban inhibits thrombus formation by inhibiting thrombin generation. Apixaban has no direct effect on platelet aggregation.

In healthy volunteers apixaban has a half-life of 12 hours and 27% is cleared via the kidney.

Who is it for?
Apixaban is indicated for prevention of stroke or systemic embolism in people with NVAF and at least one additional risk factor, as described in the listing restriction, which would place them at a moderate to high risk for stroke and/or systemic embolism.
Apixaban is an alternative to warfarin for the primary prevention of stroke in people with NVAF who are deemed to be at moderate to high risk of a thromboembolic event. Dabigatran and rivaroxaban are also alternatives to warfarin in these people.

**How does it compare?**

At present there are no head-to-head trials comparing the relative efficacy and safety of apixaban, rivaroxaban and dabigatran.

Apixaban has been compared with INR-adjusted warfarin for stroke prevention in patients with NVAF and at least one additional risk factor for stroke in the key study, ARISTOTLE, a double-blind, double-dummy, randomised controlled trial of 18,201 patients.

Apixaban has also been compared with aspirin for stroke prevention in NVAF in the AVERROES study. The AVERROES study was terminated early when an independent committee found clear evidence of superior efficacy and safety of apixaban over aspirin.

However, as this study was conducted with a comparator that would not be recommended for patients with NVAF who are at moderate to high risk of stroke, this review focusses only on the ARISTOTLE study.

The primary objective of the ARISTOTLE study was to determine whether apixaban was non-inferior to warfarin (target INR 2.0–3.0) at reducing the combined outcome of stroke (ischaemic or haemorrhagic) and systemic embolism.

The secondary outcomes were to determine whether apixaban was superior to warfarin for the combined endpoint of stroke, systemic embolism and all-cause mortality. The primary safety endpoint was incidence of major bleeding.

The study recruited 18,201 patients, mainly men (65%), from 1034 sites in 39 countries. Patients were included in the trial if they were over 18 years with permanent or persistent NVAF and one additional risk factor for stroke (≥ 75 years, prior stroke or TIA, symptomatic chronic heart failure, diabetes mellitus, or hypertension requiring pharmacological treatment).
The exclusion criteria included increased bleeding risk such as:

- previous intracranial haemorrhage
- recent history of stroke (within 7 days)
- conditions that required chronic anticoagulation such as prosthetic valve placement
- renal insufficiency (CrCl < 25 mL/min).

The main qualifying risk factor for inclusion in the trial was hypertension (87%) and the mean CHADS₂ score at randomisation was 2.1 ± 1.1.

The median age was 70 and most patients had an NVAF diagnosis of persistent or permanent (85%).

Most patients had also used vitamin K antagonists for > 30 days (57%) at randomisation and most were also taking other medicines such as ACE inhibitors (71%), beta blockers (64%) or statins (45%).

Most patients had normal (CrCl > 80 mL/min, 41.2%) or mildly impaired renal function (50–80 mL/min, 42%).

A recent analysis of the ARISTOTLE population indicated that it is broadly representative of ‘real world’ NVAF patients. Apixaban is associated with fewer strokes than warfarin

In the ARISTOTLE trial the incidence of stroke or systemic embolism was 212 (1.27% per year) in patients treated with apixaban compared with 265 (1.60% per year) in patients treated with warfarin (Table 1).

This was a statistically significant result demonstrating that apixaban was superior to warfarin in preventing thromboembolic events, in particular, haemorrhagic stroke in people with NVAF (p = 0.01 for superiority).

The rate of haemorrhagic stroke was significantly lower (49% reduction, p < 0.001) with apixaban compared with warfarin, but for ischaemic stroke there was a non-significant reduction (8%, p = 0.42). Apixaban was also associated with a reduction in death from any cause but not occurrence of MI.
Incidence of strokes consistent across subgroups

Subgroup analyses were undertaken in a number of pre-specified groups.6,11,12 The reduction in primary efficacy outcome was consistent across all subgroups analysed, with no statistically significant differences detected.6

In particular, patients stratified by renal function (normal: CrCl > 80 mL/min; moderate dysfunction: 50–80 mL/min; severe dysfunction: < 50 mL/min) showed no differences between groups for efficacy of apixaban.11

In all subgroups, apixaban was associated with fewer strokes or systemic emboli, although patients in both treatment arms with worse renal function tended to have more events.11

The primary outcome of stroke reduction was also independent of stroke risk or bleeding risk. In patients stratified by stroke risk (CHADS2 or CHA2DS2-VASc score) and bleeding risk (HAS-BLED score) apixaban was associated with fewer strokes or systemic emboli compared with warfarin.12

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Apixaban group (n = 9120)</th>
<th>Warfarin group (n = 9081)</th>
<th>Hazard ratio [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event (n)</td>
<td>Event rate (%/year)</td>
<td>Patients with event (n)</td>
<td>Event rate (%/year)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>212</td>
<td>1.27</td>
<td>265</td>
<td>1.60</td>
</tr>
<tr>
<td>- Stroke</td>
<td>199</td>
<td>1.19</td>
<td>250</td>
<td>1.51</td>
</tr>
<tr>
<td>- Ischaemic or uncertain stroke</td>
<td>162</td>
<td>0.97</td>
<td>175</td>
<td>1.05</td>
</tr>
<tr>
<td>- Haemorrhagic stroke</td>
<td>40</td>
<td>0.24</td>
<td>78</td>
<td>0.47</td>
</tr>
<tr>
<td>- Systemic embolism</td>
<td>15</td>
<td>0.09</td>
<td>17</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key secondary efficacy outcome: death from any cause</td>
<td>603</td>
<td>3.52</td>
<td>669</td>
<td>3.94</td>
</tr>
<tr>
<td><strong>Other secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or death from any cause</td>
<td>752</td>
<td>4.49</td>
<td>837</td>
<td>5.04</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>90</td>
<td>0.53</td>
<td>102</td>
<td>0.61</td>
</tr>
<tr>
<td>Stroke, systemic embolism, MI, or death from any cause</td>
<td>810</td>
<td>4.85</td>
<td>906</td>
<td>5.49</td>
</tr>
<tr>
<td>Pulmonary embolism or DVT</td>
<td>7</td>
<td>0.04</td>
<td>9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

CI: confidence interval    NS: non-significant
Apixaban is associated with fewer major bleeds

There was a statistically significant reduction in major bleeding (p < 0.001) in patients treated with apixaban compared with patients treated with warfarin. Major bleeding occurred in 327 patients treated with apixaban (2.13% per year) during the 1.8-year follow-up compared with 462 patients treated with warfarin (3.09% per year) (Table 2).

The reduction in major bleeding was consistent across most subgroups analysed. Patients with CrCl ≤ 50 mL/min had fewer major bleeding events when treated with apixaban (n = 73) compared with warfarin (n = 142) (hazard ratio 0.50, 95% CI 0.38 to 0.66, p = 0.005). Patients with the worst renal function made up 17% of the trial population, and 24.3% of these were also taking a lower dose of apixaban. This may have affected the results; it is unknown whether a lower dose of apixaban will be associated with lower rates of bleeding independent of renal function.

Greater reduction in bleeding with apixaban was also seen in patients without diabetes compared with patients with diabetes (p value for interaction = 0.003). Patients with diabetes had a similar bleeding event rate between warfarin (3.1% event rate) and apixaban (3.0% event rate) groups.

Patients with the worst stroke and bleeding risk scores at randomisation had more bleeding events overall. However, no differences in treatment effect were seen between the patients with the lowest versus highest risk scores.

No effect of time in therapeutic range in the warfarin group

During the 1.8-year follow-up, patients in the warfarin treatment group had a mean INR in the therapeutic range (2.0–3.0) 62.2% of the time.

Table 2: Bleeding outcomes and net clinical outcomes of ARISTOTLE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Apixaban group (n = 9088)</th>
<th>Warfarin group (n = 9052)</th>
<th>Hazard ratio [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary safety outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>327</td>
<td>2.13</td>
<td>462</td>
<td>3.09</td>
</tr>
<tr>
<td>~ Intracranial</td>
<td>52</td>
<td>0.33</td>
<td>122</td>
<td>0.80</td>
</tr>
<tr>
<td>~ GI</td>
<td>105</td>
<td>0.76</td>
<td>119</td>
<td>0.86</td>
</tr>
<tr>
<td>~ Other</td>
<td>275</td>
<td>1.79</td>
<td>340</td>
<td>2.27</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>613</td>
<td>4.07</td>
<td>877</td>
<td>6.01</td>
</tr>
<tr>
<td><strong>Net clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism, or major bleeding</td>
<td>521</td>
<td>3.17</td>
<td>666</td>
<td>4.11</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleeding or all-cause mortality</td>
<td>1009</td>
<td>6.13</td>
<td>1168</td>
<td>7.20</td>
</tr>
</tbody>
</table>
In a post-hoc analysis of the ARISTOTLE findings time in the therapeutic range had no effect on the primary efficacy and safety endpoints, consistent with the main findings. However, as this was a post-hoc analysis these results require confirmation in further studies.

A recent audit of 1137 Tasmanian patients taking warfarin over a 3.5-year period (2007–2010) demonstrated a comparable mean time in the therapeutic range of 69.1%, indicating that the ARISTOTLE study population may be broadly representative of that seen in clinical practice in Australia.

Key findings
Overall, the key findings for the ARISTOTLE study demonstrate that apixaban is more effective than warfarin in preventing the primary efficacy outcome of stroke or systemic embolism over a median follow-up period of 1.8 years and that bleeding events are less likely in patients taking apixaban than in those taking warfarin.

When reduction in stroke and systemic embolism is combined with major bleeding events the net clinical benefit of apixaban is superior to that of warfarin (Table 2, p < 0.001). Apixaban reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31% and death by 11%. For every 1000 patients treated with apixaban instead of warfarin for 1.8 years six strokes, 15 major bleeds and eight deaths would be prevented.

Direct comparisons assessing the relative efficacy of apixaban, rivaroxaban and dabigatran compared with that of warfarin are currently not available. There are considerable differences between the major trials for each of these newer anticoagulants in terms of populations studied, trial design and statistical outcome measures.

While all appear to be as effective as warfarin in preventing stroke in people with NVAF, no conclusions can be made about how they compare with each other. If an alternative to warfarin is required, choice should therefore be guided by clinical judgement, individual patient characteristics and preference, and agent characteristics.

Safety issues
No antidote and no measure of coagulation
As with the other newer oral anticoagulants, balance the efficacy and safety of apixaban against the lack of monitoring assays to determine whether a patient is being over-anticoagulated or whether they are compliant with therapy. There is currently no clinically verified antidote aside from cessation of therapy.

No safety data beyond 1.8 years
The safety of apixaban was studied in the ARISTOTLE study in 9088 patients for a median time of 1.8 years. Safety beyond 1.8 years of continuous therapy has not been established. In addition, while the inclusion criteria in the ARISTOTLE study were largely representative of the usual NVAF population, there are a number of important populations in which the safety of apixaban has not been established, such as those requiring antiplatelet medicine (other than aspirin) and people aged over 75 (only small numbers in the ARISTOTLE trial).

Adverse event rates similar between groups
Overall adverse events in the ARISTOTLE trial occurred at a similar rate between the apixaban and warfarin groups (81.5% and 83.1%, respectively). Serious adverse events were also closely matched (35% for apixaban and 36.5% for warfarin). There was a 1.8% discontinuation rate due to adverse events for apixaban compared with a 2.6% rate for warfarin.

The overall incidence of adverse events related to bleeding was lower in patients taking apixaban (24.3%) compared with patients taking warfarin (31.0%) although statistical analysis of this number is not available. Apixaban was not associated with an increased incidence of GI bleeding, gingival bleeding, haematoma or epistaxis compared with warfarin.
**Bleeding risk**
The main safety concern when prescribing any oral anticoagulant is bleeding. Apixaban inhibits thrombin and increases bleeding time,1 which places patients at risk of bleeding events.

In the ARISTOTLE study patients treated with apixaban had fewer major bleeding events than patients treated with warfarin.6 This may be a positive outcome in favour of apixaban; however, major bleeding still occurs in patients treated with apixaban and there is little clinical advice about how to treat that bleeding when it occurs.2

Unlike warfarin, apixaban has no antidote and no established way to reverse the anticoagulant effect.2 Apixaban has a half-life of 12 hours, so any significant anticoagulant effect is likely to continue for at least 24 hours after the last dose.2

The Product Information contains various strategies for dealing with bleeding when it occurs;2 however, these have not been validated in the clinical setting, and this remains a concern.

**Renal and hepatic impairment**
The ARISTOTLE study showed that apixaban was effective in preventing stroke without increased bleeding in patients with renal impairment.6,11

However, there is little experience of apixaban in people with severe renal impairment (CrCl < 25 mL/min), and apixaban is therefore contraindicated in these people.2

Apixaban may be used in people with mild or moderate hepatic impairment (Child–Pugh grade A or B);6 however, as with all anticoagulants, do not use it in patients with hepatic impairment associated with coagulopathy or in patients with severe hepatic impairment (Child–Pugh grade C).6

People with elevated liver enzyme levels (ALT/AST > 2 ULN or total bilirubin ≥ 1.5 ULN) were excluded from the ARISTOTLE trial. The Product Information advises caution in these patients and recommends that liver function be determined before starting apixaban.2

**Interaction with common medicines**
As with all anticoagulants, use caution when prescribing apixaban with any other medicine known to affect haemostasis, including other anticoagulants, antiplatelet agents, aspirin and NSAIDs. SSRIs and SNRIs should also be prescribed with caution. St John’s wort and grapefruit juice may also interact with apixaban. For more information on important interactions with common medicines refer to the Product Information.

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed three times a year with Australian Prescriber.

**Reason for PBAC recommendation**
The PBAC recommended the listing of apixaban on the PBS for the prevention of stroke in patients with NVAF on a cost-minimisation basis compared with rivaroxaban, with the equi-effective dose based on doses in the trials, and PBS restriction.

**Dosing issues**
The recommended dose of apixaban for stroke prevention in NVAF is 5 mg twice daily.

Apixaban can be taken with or without food. Missed doses should be taken as soon as possible on the same day and twice-daily administration resumed thereafter.2 Taking a double dose of apixaban is not advised.

**Lower dose required in certain populations**
A lower dose of 2.5 mg twice daily is recommended in people with at least two of the following:

- age ≥ 80 years
- body weight ≤ 60 kg
- serum creatinine ≥ 133 micromol/L.2

ALT: alanine aminotransferase    AST: aspartate aminotransferase
ULN: upper limit of normal    NSAIDs: non-steroidal anti-inflammatory drugs
SSRIs: selective serotonin reuptake inhibitors    SNRIs: serotonin-noradrenaline reuptake inhibitors
Switching between oral anticoagulants
There is currently little clinical experience in switching between oral anticoagulants. Consult the Product Information for advice regarding switching people from warfarin to apixaban, or switching from apixaban to warfarin.2

Surgery and invasive procedures
Apixaban should be discontinued 48 hours before elective surgery or other invasive procedures that have a moderate or high risk of bleeding. In particular, placement of spinal or epidural anaesthesia is associated with a risk of haematoma which can result in long-term or permanent paralysis.2

For procedures with low risk of bleeding, discontinuation of apixaban is advised 24 hours prior. However, stopping anticoagulant therapy may put people at risk of stroke — use clinical judgement when advising patients about stopping therapy for minor surgery such as dental treatment.

Pregnancy, lactation and paediatric use
Apixaban is not recommended in pregnancy — use of anticoagulants in pregnancy can result in placental haemorrhage. Apixaban should not be used in lactating women, as it may be excreted in human milk, and risk to infants cannot be excluded. Apixaban has not been assessed in children and adolescents and is not recommended for anyone under 18.2

Medicine interactions
Apixaban is metabolised mainly via CYP3A4/5 and is a substrate of the efflux transport protein, P-glycoprotein (P-gp). Co-administration of strong inhibitors of CYP3A4 and P-gp is contraindicated.

No dose adjustment is required when co-administering other medicines that are not considered strong inhibitors of CYP3A4 and P-gp (e.g. verapamil, clarithromycin or amiodarone).

Strong inducers of CYP3A4 and P-gp should be co-administered with caution. Refer to the Product Information for specific prescribing advice.2

Possible interactions

Information for patients
Ensure that patients are aware that they may experience bleeding while taking apixaban. Patients should be told to recognise the signs of serious internal bleeding such as unexplained bruising, blood in the urine or black stools.

Advise patients:

- to consult their doctor if they experience any prolonged or excessive bleeding
- that apixaban is taken twice daily with food
- that, while there is no need for the continued monitoring associated with warfarin therapy, there is also no way to confirm anticoagulant effect and no way to reverse bleeding. Advise patients to be extra-vigilant for signs of bleeding.

Ensure patients understand that they should consult a doctor before taking non-prescription medicines containing aspirin or NSAIDs. Paracetamol may be used.

Patients should inform healthcare professionals, including dentists and pharmacists, that they are taking apixaban.

REFERENCES


Revision history

Updated mid-August 2013 to reflect PBS listing for this indication.
First published: 1 August 2013 (as PBAC recommended for PBS listing for this indication).

The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.