The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Apixaban is an oral, direct factor Xa inhibitor that is FDA approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).

- **Stroke prevention in AF dosing:** Apixaban is available in 2.5 mg and 5 mg unscored tablet strengths. The recommended dose of apixaban is 5 mg orally twice daily for most patients (with or without food). A reduced dose of 2.5 mg orally twice daily is recommended for patients with 2 or more of the following: age ≥80 years; weight ≤60 kg; serum creatinine (SCr) ≥1.5 mg/dL. Clinical data are lacking on the use of apixaban in patients with a SCr >2.5 mg/dL or creatinine clearance (CrCl) <25 ml/min, since these patients were excluded from pivotal clinical trials.

- **Efficacy and Bleeding in Stroke Prevention in AF:** Apixaban was studied in 2 phase 3 studies for the reduction of stroke and systemic embolism in patients with nonvalvular AF. The primary support for FDA approval was obtained from the ARISTOTLE trial, a randomized, double-blind, multinational, noninferiority trial where apixaban was compared to warfarin. Supportive information for the AF indication was provided by the AVERROES trial, a randomized, double-blind, multinational superiority trial where apixaban was compared to aspirin in patients considered unsuitable for warfarin.

In ARISTOTLE, 18,201 patients with a mean CHADS2 score of 2.1 were randomized to receive apixaban 5 mg twice daily or adjusted dose warfarin once daily with a goal International Normalized Ratio (INR) of 2-3. A reduced dose of apixaban (2.5 mg twice daily) was administered to 4.7% of patients with at least 2 of the following: age of at least 80 years, body weight of 60 kg or less, or SCr level of 1.5 mg/dL or greater. Following noninferiority testing for the primary endpoint, prespecified, hierarchical sequential testing was conducted for superiority on the primary endpoint, major bleeding, and all-cause mortality. The median age of the study population was 70 years, with about 31% of patients aged 75 or older. The mean time in therapeutic range with warfarin was 62%, and average duration of follow-up was 1.8 years.

For the primary endpoint of reduction in stroke and systemic embolism, apixaban was found to be noninferior and also superior to warfarin, with event rates of 1.27% per year with apixaban and 1.6% per year with warfarin (HR 0.79; 95% CI 0.66-0.95), with the results driven primarily by a reduction in hemorrhagic stroke with apixaban (annual rates of 0.24% vs. 0.47%; HR 0.51; 95% CI 0.35-0.75). Apixaban was associated with significantly lower rates of major bleeding compared to warfarin (2.1% per year vs. 3.1% per year; HR 0.69; 95% CI 0.6-0.8). A borderline statistically significant mortality benefit was found with apixaban (3.52% per year with apixaban vs. 3.94% per year with warfarin; HR 0.89; 95% CI 0.8-0.998; p=0.047). Other secondary composite endpoints were favorable for apixaban. Per subgroup analysis, the treatment effect of apixaban appears to be consistent across multiple subgroups including patients 75 years of age and older and those with renal impairment.

In the AVERROES trial, apixaban 5 mg twice daily was found to be superior to aspirin 81-324 mg daily for the primary composite endpoint of stroke and systemic embolism (1.6% per year vs. 3.7% per year [HR 0.45; 95% CI 0.32-0.62]) with a similar risk of major bleeding (1.4% per year with apixaban vs. 1.2% per year with aspirin; HR 1.13; 95% CI 0.74-1.75; p=0.57). There was no excess of intracranial, gastrointestinal, or fatal bleeding with apixaban compared to aspirin, though rates of minor bleeding were significantly higher with apixaban. A favorable trend in mortality was noted with apixaban (annual rates of 3.5% vs. 4.4%; HR 0.79; 95% CI 0.62-1.02; p=0.07). The net clinical benefit, considering stroke and vascular events along with major bleeding, was favorable for apixaban (5.3% per year with apixaban vs. 7.2% per hear with aspirin; HR 0.74;
95% CI 0.6-0.9). Per subgroup analysis, the treatment effect of apixaban appears to be consistent across multiple groups including patients with history of previous TIA/stroke, renal impairment, and age of 75 years or older. The trial was stopped early due to the apparent benefit of apixaban upon planned interim analysis.

- Apixaban is contraindicated in patients with active pathological bleeding and history of a severe hypersensitivity reaction to the drug.
- **Boxed Warning - Discontinuation in patients with AF:** Patients are at increased risk of thrombotic events when apixaban is discontinued in the absence of alternative adequate anticoagulation. A 4-fold increased risk of stroke compared to warfarin was observed in clinical trials in patients with AF in the 30 days after stopping study drug. If apixaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
- The major risk with apixaban treatment is bleeding. Bleeding complications were the most commonly reported adverse events. In the ARISTOTLE trial, there were significantly fewer major bleeding events in patients on apixaban compared to warfarin (2.13% per year vs. 3.09% per year; HR 0.69; 95% CI 0.6-0.8), including intracranial bleeds (0.33% per year vs. 0.8% per year; HR 0.42; 95% CI 0.3-0.58). Rates of gastrointestinal bleeding were similar between groups. In looking at major bleeding according to baseline characteristics, the advantage of apixaban was maintained across most subgroups.
- Routine coagulation monitoring of apixaban is not required based on the stable pharmacokinetic and pharmacodynamic properties of the drug. There is no known reversal agent or antidote for apixaban, though the drug has a shorter duration of action compared to warfarin. Unlike warfarin, data on the optimal management of bleeding, including major and life-threatening bleeding, with apixaban is lacking. General hemostatic measures should be employed.
- The safety and efficacy of apixaban has not been studied in patients with prosthetic heart valves and use of apixaban is not recommended.
- Apixaban is a substrate of CYP3A4 and P-gp. Inhibitors of CYP3A4 and/or P-gp will increase or decrease apixaban exposure, respectively. Concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) should be avoided due to decreased apixaban exposure and potential reduced effectiveness. The manufacturer recommends a dose reduction to 2.5 mg twice daily when apixaban is used concomitantly with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) based on pharmacokinetic studies demonstrating increased exposure. Further, in patients already receiving the reduced dose of apixaban because of patient characteristics should avoid the concurrent use of strong dual CYP3A4 and P-gp inhibitors with apixaban.
- Concomitant use of apixaban and medications that affect hemostasis are expected to increase the risk of bleeding (aspirin, anti-platelet agents, other antithrombotic agents, fibrinolytics, NSAIDs). In an acute coronary syndrome (ACS) population, apixaban was associated with a significantly increased risk of bleeding when added to aspirin plus a P2Y12-receptor antagonist (mostly clopidogrel) or aspirin alone.
- Apixaban has also been studied for venous thromboembolism (VTE) prophylaxis, VTE treatment, and ACS. These indications remain off-label at this time.

**Introduction**

Apixaban is an oral, direct factor Xa inhibitor approved in the US for the prevention of stroke and systemic embolism in patients with nonvalvular AF.

Generally attributed to embolism of thrombus from the left atrium, patients with AF are at a 4-5 fold increased risk of stroke and systemic embolism compared to those without AF.\(^1\,\text{,}\,\text{2}\) Annual rates of stroke in patients with AF are estimated to be between 3-8%, depending on additional risk factors.\(^1\) Several clinical risk stratification schemes have been developed to assess the stroke risk in AF, including the commonly used CHADS\(_2\) score and CHADS\(_2\)VASc score.\(^3\,\text{,}\,\text{4}\)

**Risk of stroke by CHADS\(_2\) score:**\(^5\)
**CHADS2 Score**

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Adjusted Stroke Rate % per yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>5 or 6</td>
<td>6.9</td>
</tr>
</tbody>
</table>

The CHADS2 score is the sum of points assigned for different risk factors. One point each is given for the following: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus; two points are given for history of stroke or transient ischemic attack.

Options for oral antithrombotic treatment for the reduction of stroke and systemic embolism related to AF have traditionally included warfarin and antiplatelet agents. Several, high quality, randomized, controlled trials and meta-analyses have evaluated the effectiveness of these agents. While both warfarin and antiplatelet agents have been shown to be effective in reducing risk of stroke, warfarin has been shown to be consistently and significantly more effective than placebo or aspirin. Aspirin is associated with risk reductions of about 20% compared to placebo, whereas warfarin is associated with risk reductions of about 60-70% vs. placebo and about 50% compared to aspirin.¹,⁶,⁷

Newly available agents in the US include dabigatran, rivaroxaban, and apixaban. These agents exhibit predictable pharmacodynamic effects and do not require routine laboratory monitoring of their anticoagulant effect. The advantage of improved convenience for patients must be balanced with the lack of long term safety data and availability of a reversal agent. Dabigatran (in the FDA approved dose) was found to be at least as effective as and possibly more effective than warfarin in the reduction of stroke or systemic embolism with similar rates of major bleeding. The efficacy advantage of dabigatran over warfarin appears to be less in the setting of better INR control. Rivaroxaban was found to be noninferior to warfarin in reducing the risk of stroke and systemic embolism with similar rates of major bleeding in a higher risk patient population (e.g., higher CHADS² score) with INR control that was suboptimal. The new oral anticoagulants have been consistently associated with significantly lower rates of intracranial bleeding compared to warfarin.

The decision to initiate antithrombotic therapy should be based on assessment of the individual patient’s risk of embolic event without therapy and risk of bleeding with therapy. Choice of agent (e.g., warfarin, aspirin, or other) should be based upon the absolute risks of stroke and bleeding and relative risk and benefit for a given patient.²

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating apixaban for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

**Pharmacology/Pharmacokinetics/Pharmacodynamics**

- Apixaban is an oral factor Xa inhibitor that selectively blocks the active site of Xa and does not require a co-factor. Apixaban lowers the risk of blood clots by inhibiting both free and clot bound factor Xa and prothrombinase activity. Apixaban indirectly inhibits platelet aggregation induced by thrombin.

**Table 1. Pharmacokinetics of apixaban, dabigatran, and rivaroxaban**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>50% (unaffected by food); prolonged absorption</td>
<td>3 – 7%</td>
<td>10 mg dose: 80-100% (unaffected by food)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>3-4 hrs</td>
<td>1.2 hrs</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>87%</td>
<td>35%</td>
<td>92-95%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4 (major); CYP1A2, 2C8, 2C9, 2J2 (all minor)</td>
<td>Conjugation</td>
<td>CYP3A4/5, CYP2J2, hydrolysis</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal (27%), fecal</td>
<td>Renal (80%)</td>
<td>Renal (66%; 36% as unchanged drug)</td>
</tr>
<tr>
<td>Half-life</td>
<td>12 hrs</td>
<td>12 – 17 hrs</td>
<td>5-9 hrs*</td>
</tr>
</tbody>
</table>

*Half-life is increased to 11-13 hrs in the elderly

Updated version may be found at www.pbm.va.gov or vaww.pbm.va.gov
Apixaban prolongs clotting tests including the prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT); however, the effects are highly variable. Therefore, the manufacturer does not recommend using these tests as a measure of effectiveness for apixaban.

Upon repeat dosing, anticoagulation persists for at least one day. (See Dosage and Administration for more information on discontinuation for surgery/procedures.)

Apixaban is metabolized primarily by CYP3A4, with CYP1A2, 2C8, 2C9, 2C19, and 2J2 playing minor roles. There are no active circulating metabolites. Apixaban is a substrate of the transporter proteins P-glycoprotein (gp) and breast cancer resistance protein.

About 27% of apixaban is eliminated through renal excretion. Biliary and direct intestinal excretion contributes to the elimination in the feces.

**FDA Approved Indication(s)**

Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.

**Potential Off-label Uses**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](https://www.va.gov/pbm) (available on the VA PBM Intranet site only).

Apixaban has been studied or is undergoing study for several indications including VTE treatment, VTE prophylaxis in medically ill patients, VTE prophylaxis in patients undergoing orthopedic surgery, and ACS. Further details are provided in the Efficacy section.

**Current VA National Formulary Alternatives**

Aspirin, dabigatran, and warfarin are on VA National Formulary. Dabigatran is restricted to Criteria for Use.

**Dosage and Administration**

Apixaban is available in 2.5 mg and 5 mg unscored tablet strengths.

**Usual Dose**

The recommended dose of apixaban is 5 mg orally twice daily for most patients (with or without food).

**Dosage Reductions**

A reduced dose of 2.5 mg orally twice daily is recommended for patients with 2 or more of the following:

- Age of 80 years or greater
- Body weight of 60 kg or less
- Serum creatinine of 1.5 mg/dL or greater

**Use with Strong Dual CYP3A4 and P-gp Inhibitors or Inducers**

A reduced dose of 2.5 mg orally twice daily is recommended for patients on concomitant therapy with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) due to increased apixaban exposure and potential for increase bleeding risk. For patients already receiving the reduced dose of 2.5 mg twice daily, concomitant use of strong dual inhibitors of CYP3A4 and P-gp should be avoided.
Concomitant use of strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, St. John’s wort, carbamazepine, and phenytoin) should be avoided due to decreased apixaban exposure and potentially reduced effectiveness.

**Surgery and Interventions**
Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with low bleeding risk or where the bleeding would be in a non-critical location and easily controlled. For other invasive procedures and surgeries where the bleeding risk is moderate to high or where bleeding could be unacceptable, apixaban should be discontinued at least 48 hours prior to the procedure or surgery.

**Switching from and to warfarin**
When switching from warfarin to apixaban, the manufacturer recommends starting apixaban when the INR is below 2. When switching from apixaban to warfarin, consider that apixaban affects the INR so that measurements taken during the transition to warfarin may not be helpful in titrating the warfarin dose. Consider discontinuing apixaban and starting a parenteral anticoagulant along with warfarin at the time the next dose of apixaban would be due. Discontinue the parenteral anticoagulant when the INR on warfarin is therapeutic.

**Switching from or to anticoagulants other than warfarin**
Discontinue the anticoagulant being used and start the other at the next scheduled dose.

**Missed Dose**
If a dose is missed, administer the missed dose as soon as possible on the same day and resume twice daily administration. Doses should not be doubled.

**Discontinuation**
If apixaban must be discontinued for reasons other than pathological bleeding, consider administering another anticoagulant. Discontinuing apixaban in the absence of adequate alternative anticoagulation increases the risk of thrombotic events (e.g., stroke). (See Boxed Warnings)

**Renal impairment**
The dose of apixaban should be reduced to 2.5 mg twice daily in patients with 2 or more of the following: a serum creatinine of 1.5 mg/dL or higher, age of 80 years or older, or body weight of 60 kg or less, which is the dose modification that was used during clinical trials. Clinical data are lacking on the use of apixaban in patients with a SCr greater than 2.5 mg/dL or CrCl less than 25 ml/min, since these patients were excluded from pivotal studies.

**Hepatic impairment**
No dose adjustment is needed in patients with mild hepatic impairment. Patients with moderate hepatic impairment were excluded from clinical studies because these patients may have intrinsic coagulation abnormalities. Therefore, no dosing recommendations are available. Use of apixaban is not recommended in patients with severe hepatic impairment.

**Crushing tablets**
Based on pharmacokinetic studies in healthy volunteers, the bioavailability of apixaban crushed tablets appears to be similar to that of apixaban tablets. 11

**Efficacy**
Apixaban has been studied in 2 phase 3 studies and is FDA approved for the reduction of stroke and systemic embolism in patients with nonvalvular AF. FDA approval was based mainly on data from the pivotal ARISTOTLE trial, where apixaban was compared to warfarin. 12, 13 Supportive information for the AF indication was provided by the AVERROES trial, where apixaban was compared to aspirin in patients considered unsuitable for warfarin. 14, 15 Apixaban has also been studied for the following off-label indications: VTE treatment, VTE prophylaxis in medically ill patients, VTE prophylaxis in orthopedic surgery patients, and ACS. Efficacy results are summarized below according to indication.

**Stroke and systemic embolism prevention in nonvalvular AF (FDA Approved)**
Outcome Measures:
Primary Efficacy Endpoint: Composite of stroke (ischemic, hemorrhagic or uncertain type) and systemic embolism

Secondary Endpoints: major bleeding, all-cause death; myocardial infarction (MI); composite of stroke, systemic embolism or all-cause death; composite of stroke, systemic embolism, MI, or all-cause death; PE or DVT.

ARISTOTLE
The effect of apixaban on reducing the risk of stroke or systemic embolism in patients with nonvalvular AF was compared to warfarin in the phase 3, randomized, double-blind, multinational, non-inferiority ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. A total of 18,201 patients with a mean CHADS2 score of 2.1 were randomized to receive blinded treatment with apixaban 5 mg twice daily or adjusted dose warfarin (goal INR of 2-3) once daily. A reduced dose of apixaban (2.5 mg twice daily) was administered to 4.7% of patients with at least 2 of the following: age of at least 80 years, body weight of 60 kg or less, or SCr of 1.5 mg/dL or greater. Following noninferiority testing for the primary endpoint, prespecified, hierarchical sequential testing was conducted for superiority on the primary endpoint, then on major bleeding, and then on all-cause mortality. The median age of the study population was 70 years, with about 31% of patients aged 75 or older. Forty-three percent of patients were vitamin K antagonist naïve, 19% had a prior transient ischemic attack (TIA) or stroke, and 31% of patients were on aspirin. The distribution of patients with CHADS2 scores of 1, 2, or 3 or more were evenly distributed, with about one third of patients in each group. The mean time in therapeutic range with warfarin was 62%, and average duration of follow-up was 1.8 years. About one quarter of the patients randomized discontinued treatment before the end of the study (fewer in apixaban arm).

For the primary endpoint, apixaban was found to be noninferior and also superior to warfarin, with event rates of 1.27% per year with apixaban and 1.6% per year with warfarin (HR 0.79; 95% CI 0.66-0.95). The difference in the rates for the composite primary endpoint between treatment groups was driven primarily by a reduction in hemorrhagic stroke with apixaban (annual rates of 0.24% vs. 0.47%; HR 0.51; 95% CI 0.35-0.75), with no difference on ischemic stroke. Apixaban was associated with significantly lower rates of major bleeding compared to warfarin (2.1% per year vs. 3.1% per year; HR 0.69; 95% CI 0.6-0.8). A borderline statistically significant mortality benefit was found with apixaban (3.52% per year with apixaban vs. 3.94% per year with warfarin; HR 0.89; 95% CI 0.8-0.998; p=0.047). Other secondary composite endpoints were favorable for apixaban, and there were no differences found in rates of MI, DVT, or PE between treatment groups. Per subgroup analysis, the treatment effect of apixaban appears to be consistent across multiple subgroups including patients 75 years of age and older and those with renal impairment.

Selected Outcomes From ARISTOTLE with Apixaban and Warfarin

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>APIX  N=9120 (% per yr)</th>
<th>WARF N=9081 (% per yr)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Endpoint: Composite of stroke (ischemic or hemorrhagic) or SE</td>
<td>212 (1.27)</td>
<td>265 (1.6)</td>
<td>0.79 (0.66-0.95)</td>
<td>0.01</td>
<td>303</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>40 (0.24)</td>
<td>78 (0.47)</td>
<td>0.51 (0.35-0.75)</td>
<td>&lt;0.001</td>
<td>435</td>
</tr>
<tr>
<td>Ischemic stroke or uncertain type</td>
<td>162 (0.97)</td>
<td>175 (1.05)</td>
<td>0.92 (0.74-1.13)</td>
<td>0.42</td>
<td>-</td>
</tr>
<tr>
<td>SE</td>
<td>15 (0.09)</td>
<td>17 (0.1)</td>
<td>0.87 (0.44-1.75)</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>90 (0.53)</td>
<td>102 (0.61)</td>
<td>0.88 (0.66-1.17)</td>
<td>0.37</td>
<td>-</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>603 (3.52)</td>
<td>669 (3.94)</td>
<td>0.89 (0.8-0.998)</td>
<td>0.047</td>
<td>238</td>
</tr>
</tbody>
</table>

†Efficacy endpoints based on intention-to-treat (ITT) population; major bleeding outcome and 2nd composite outcomes based on the population that received at least one dose of study drug; NNT=number needed to treat; SE=systemic embolism

Treatment effects based on INR control
Analyses were conducted to evaluate the impact of the quality of the center’s INR control on study outcomes. Information is limited to unpublished data available from the manufacturer and the FDA medical review. The mean
time in therapeutic range (TTR) from ARISTOTLE was 62%, which is within the range of the mean TTR reported from other contemporary major clinical trials. Findings from both the manufacturer and FDA suggested that the overall effects for apixaban on the primary composite endpoint of reduction in stroke and systemic embolism were fairly consistent across a wide range of center TTR quartiles. Apixaban was associated with lower rates of major bleeding compared to warfarin regardless of the quality of INR control. There appeared to be a relationship between quality of INR control and all cause death, with the advantage of apixaban over warfarin most apparent at centers with lower TTR.17

**Time to events in patients discontinuing treatment**16,17
There was about a 4-fold excess of primary endpoint events, primarily ischemic stroke, which occurred within 30 days following discontinuation of study drug in patients on apixaban compared to warfarin (21 events vs. 5 events; HR 4.07; 95% CI 1.54-10.81). Nearly all of the events occurred within days 3-30. (See Safety section, Other Adverse Events)

**Patients undergoing cardioversion**16
Cardioversion procedures during the ARISTOTLE trials were allowed based on the discretion of the provider. In an unpublished analysis, 757 patients underwent cardioversion during the trial (338 apixaban patients and 419 warfarin patients). Frequencies of clinical outcomes (stroke or systemic embolism, MI, major bleeding, or death) during the 30 days post cardioversion were low and similar between treatment groups.

**Outcomes based on dose**17
About 5% of patients in ARISTOTLE received the reduced dose of 2.5 mg of apixaban twice daily based on the presence of least 2 of the following characteristics: age ≥80 years, weight ≤60 kg, or SCr ≥1.5 mg/dL. In designing the study, the lower dose was selected to be used in patients deemed at increased risk of bleeding. Examination of the primary endpoints by dose suggests that the safety and effectiveness with the lower dose is maintained.

<table>
<thead>
<tr>
<th>ARISTOTLE 1° Efficacy and Safety Endpoints by Dose</th>
<th>n</th>
<th>APIX % per year</th>
<th>WARF % per year</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or SE</td>
<td>2.5 mg BID</td>
<td>424</td>
<td>1.7</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>5 mg BID</td>
<td>8664</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Major bleed</td>
<td>2.5 mg BID</td>
<td>424</td>
<td>3.3</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>5 mg BID</td>
<td>8664</td>
<td>2.1</td>
<td>3</td>
</tr>
</tbody>
</table>

**AVERROES**
The effect of apixaban compared to aspirin in patients who were considered unsuitable for warfarin was evaluated in the similarly designed AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment).14 AVERROES was a multicenter, international, randomized, double-blinded, controlled superiority study where 5599 patients with nonvalvular AF and an additional risk factor for stroke were randomized to apixaban 5 mg twice daily or aspirin 81-324 mg once daily. A reduced dose of apixaban (2.5 mg twice daily) was administered to 6% of patients with at least 2 of the following: age of at least 80 years, body weight of 60 kg or less, or SCr of 1.5 mg/dL or greater. The study population had a mean age of 70 years and a baseline CHADS2 score of 2. About 75% of patients were on aspirin within 30 days of screening. The study was terminated early when results from the planned interim analyses showed a clear benefit of apixaban, providing a mean duration of follow-up of 1.1 years.

For the primary composite endpoint, apixaban was found to be superior to aspirin, with annual event rates of 1.6% vs. 3.7% (HR 0.45; 95% CI 0.32-0.62), driven primarily by a reduction in ischemic stroke. Apixaban was associated with a statistically similar rate of MI (0.8% per year with apixaban and 0.9% per year with aspirin; HR 0.86; 95% CI 0.5-1.48) and major bleeding (1.4% per year with apixaban vs. 1.2% per year with aspirin; HR 1.13; 95% CI 0.74-1.75). There was no excess of intracranial, gastrointestinal, or fatal bleeding with apixaban compared to aspirin, though rates of minor bleeding were significantly higher with apixaban. A favorable trend in mortality was noted with apixaban, but the difference did not reach statistical significance (annual rates of 3.5% vs. 4.4%; HR 0.79; 95%
Apixaban was studied for the extended treatment of VTE in the phase 3, double blind, placebo-controlled AMPLIFY-EXT trial, where patients who completed 6 to 12 months of anticoagulation for symptomatic VTE were treated for an additional 12 months. A total of 2,486 patients were randomized to apixaban 5 mg twice daily, apixaban 2.5 mg twice daily, or placebo. For the primary endpoint of recurrent, symptomatic VTE or VTE-related death, apixaban was superior to placebo in the 5 mg dose (4.2% vs. 11.6%; RR 0.36; 95% CI 0.25-0.53) and the 2.5 mg dose (3.8% vs. 11.6%; RR 0.33; 95% CI 0.22-0.48). Apixaban was not associated with an increased risk of major bleeding compared to placebo, with 1 (0.1%), 2 (0.2%), and 4 (0.5%) patients experiencing an event in the 5 mg, 2.5 mg, and placebo groups, respectively. There was a trend of more clinically relevant nonmajor bleeding with apixaban vs. placebo (4.2% 5 mg vs. 3% 2.5 mg vs. 2.3% placebo), with the difference between the 5mg apixaban and placebo arms reaching statistical significance (RR 1.82; 95% CI 1.05-3.18). The net clinical benefit, which considered symptomatic VTE events, cardiovascular events, and major bleeding, favored apixaban in both doses over placebo.

Apixaban is being evaluated for the treatment of symptomatic VTE in the phase 3, double blinded randomized AMPLIFY study. Results are not yet available.

**VTE Prophylaxis in patients undergoing total hip replacement (THR) or total knee replacement (TKR) (off-label)**

Apixaban has been evaluated in three randomized, multicenter, double-blind, active-control, non-inferiority phase 3 studies of similar design for the prevention of VTE in patients undergoing orthopedic surgery.\(^{19,20,21}\) In all three trials, apixaban 2.5 mg twice daily was compared to subcutaneous enoxaparin. The primary efficacy endpoint was the composite of total VTE (asymptomatic and symptomatic DVT, nonfatal PE) and all-cause death during treatment (ADVANCE-1) or within 2 days after the last dose of study drug (ADVANCE-2 and ADVANCE-3), and the primary safety endpoint was bleeding evaluated according to severity during the treatment period or within 2 days after the last dose of study drug. In ADVANCE-2 and ADVANCE-3, apixaban was found to be noninferior and superior to enoxaparin 40 mg once daily for the primary endpoint and secondary endpoint of major VTE with similar rates of major bleeding and clinically relevant bleeding. In contrast, apixaban failed to meet noninferiority requirements when compared to 30 mg twice daily enoxaparin, the FDA approved dose for patients undergoing knee replacement, in the ADVANCE-1 trial. Apixaban was associated with significantly fewer bleeding events compared to the twice daily enoxaparin regimen.

### Phase 3 Study Design with Apixaban for VTE Prevention in Orthopedic Surgery\(^{19,20,21}\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Treatment</th>
<th>Duration</th>
<th>N</th>
<th>Endpoints (same for all trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE-1</td>
<td>Total knee replacement</td>
<td>APIX 2.5 mg BID</td>
<td>10-14 d</td>
<td>3195</td>
<td>Primary Efficacy: composite of total VTE and all-cause mortality</td>
</tr>
<tr>
<td>ADVANCE-2</td>
<td>Total knee replacement</td>
<td>APIX 2.5 mg BID</td>
<td>10-14 d</td>
<td>3057</td>
<td>Safety: bleeding (evaluated according to severity)</td>
</tr>
<tr>
<td>ADVANCE-3</td>
<td>Total hip replacement</td>
<td>APIX 2.5 mg BID</td>
<td>32-38 d</td>
<td>5407</td>
<td></td>
</tr>
</tbody>
</table>

### Results of Phase 3 Studies with Apixaban for VTE Prevention in Orthopedic Surgery\(^{19,20,21}\)

<table>
<thead>
<tr>
<th></th>
<th>APIX</th>
<th>ENOX</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADVANCE-1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VTE + any death</td>
<td>9%</td>
<td>8.8%</td>
<td>APIX inferior to ENOX BID for efficacy</td>
</tr>
<tr>
<td>Major VTE + any death</td>
<td>2%</td>
<td>1.6%</td>
<td>Excess of PE events with APIX</td>
</tr>
<tr>
<td>Major bleeding*</td>
<td>0.7%</td>
<td>1.4%</td>
<td>Less major bleeding with APIX</td>
</tr>
<tr>
<td><strong>ADVANCE-2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VTE + any death*</td>
<td>15.1%</td>
<td>24.4%</td>
<td>APIX superior to ENOX QD for efficacy</td>
</tr>
<tr>
<td>Major VTE*</td>
<td>1.1%</td>
<td>2.2%</td>
<td>Excess of PE events with APIX</td>
</tr>
</tbody>
</table>

*Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [vaww.pbm.va.gov](http://vaww.pbm.va.gov)
VTE prophylaxis in medically ill patients (off-label)\textsuperscript{22}

The efficacy and safety of extended treatment with apixaban was compared to short term treatment with enoxaparin for the prevention of VTE in acutely ill medical patients in the phase 3, double-blinded, multicenter, randomized, controlled ADOPT study. Patients were randomized to receive apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg subcutaneous once daily for 6-14 days. For the primary composite endpoint of asymptomatic proximal vein thrombosis, symptomatic DVT, nonfatal PE, and VTE related death during the treatment period, 69\% (n=4495) of the study population was evaluable. Extended prophylaxis with apixaban was not shown to be superior to short term enoxaparin for the primary endpoint (2.7\% vs. 3.1\%; RR 0.87 95\% CI 0.62-1.23) and was associated with a 2.5 fold increase in major bleeding (0.47\% vs. 0.19\%; RR 2.58; 95\% CI 1.02-7.24). Nonmajor clinically relevant bleeding rates were similar between treatment groups. In examining the post-enoxaparin treatment phase (i.e., apixaban vs. placebo), apixaban was associated with a positive trend of reduced primary endpoint events, though the between group difference did not reach statistical significance. The authors conclude that while extended prophylaxis shows promise, further study is needed to identify which medically ill patients may benefit from treatment.

ACS (Off-label)\textsuperscript{16,23}

The efficacy and safety of the addition of full dose apixaban (5 mg twice daily) to the standard of care with aspirin or aspirin plus a P2Y\textsubscript{12}-receptor antagonist was evaluated in high risk patients with recent ACS in the phase 3, double-blinded, multicenter, randomized, placebo-controlled APPRAISE-2 study. The study was terminated early when about 7,400 patients out of the intended 10,800 patients were enrolled due to a significant increase in bleeding without a reduction in recurrent ischemic events. Patients had a median age of 67 years, and nearly all were on aspirin (97\%) plus a P2Y\textsubscript{12}-receptor antagonist (81\%), mostly clopidogrel. For the primary composite endpoint of cardiovascular death, MI, or ischemic stroke, apixaban was not shown to be superior to placebo, with annual event rates of 13.2\% with apixaban compared to 14\% with placebo (HR 0.95; 95\% CI 0.8-1.11). The risk of TIMI (Thrombolysis in MI) major bleeding was increased significantly in apixaban treated patients, with annual rates of 2.4\% vs. 0.9\% with placebo (HR 2.59; 95\% CI 1.5-4.46). Further, apixaban increased the risk of intracranial hemorrhage (0.6\% per year vs. 0.2\% per year; HR 4.1; 95\% CI 1.15-14.38). There were 5 bleeding-related deaths with apixaban and none with placebo (no p-value given).

Adverse Events (Safety Data)

Safety data for apixaban for the labeled indication of stroke prevention in nonvalvular AF was primarily derived from the phase 3 ARISTOTLE trial which compared apixaban and warfarin. Additional supportive data was provided by the phase 3 AVERROES trial that evaluated apixaban vs. aspirin in patients with nonvalvular AF who were considered unsuitable for warfarin. In total, these two studies included 11,886 patients who received apixaban for a mean duration of exposure of 89 weeks in ARISTOTLE and 59 weeks in AVERROES, with about 5\% of patients on the reduced dose of 2.5 mg twice daily.\textsuperscript{8,17} The phase 3 APPRAISE-2 study that investigated the addition of apixaban to the standard of care (aspirin and antiplatelet therapy) for the treatment of ACS provided supplemental information on the safety of concomitant use of antiplatelet agents with apixaban.\textsuperscript{17,23}

Safety data from non-AF studies appears to be consistent with the overall adverse event profile observed with apixaban in AF studies.
Deaths and Other Serious Adverse Events
In the ARISTOTLE study, there were a total of 1272 deaths. There were fewer deaths in the apixaban group than in the warfarin group (6.6% vs. 7.4%; p=0.05), with the difference driven mainly by a reduction in cardiovascular deaths with apixaban. A similar favorable trend in mortality was seen with apixaban in the AVERROES trial, though the between group difference between apixaban and aspirin was not statistically significant.

Serious adverse events in the ARISTOTLE study occurred in 35% and 37% of patients treated with apixaban and warfarin, respectively. Overall, rates of serious non-bleeding adverse events were similar between treatment groups (bleeding adverse events are discussed separately under Other Adverse Events). Syncope and dizziness were reported more frequently with apixaban than with warfarin but occurred in less than 1% of patients. There were more ischemic strokes that occurred after discontinuation of apixaban. (see Other Adverse Events)

Common Non-Bleeding Adverse Events
The most commonly reported adverse events reported in clinical trials included nasopharyngitis, dizziness, peripheral edema, dyspnea, and diarrhea. There was no excess of events reported with apixaban compared to warfarin.

Other Adverse Events

Bleeding
The major risk with apixaban treatment is bleeding. Bleeding complications were the most commonly reported adverse events. In the ARISTOTLE trial, there were significantly fewer major bleeding events in patients on apixaban compared to warfarin (2.13% per year vs. 3.09% per year; HR 0.69; 95% CI 0.6-0.8), including intracranial bleeds (0.33% per year vs. 0.8% per year; HR 0.42; 95% CI 0.3-0.58). The advantage of apixaban was observed early in the trial and persisted throughout the duration of the trial. Rates of gastrointestinal bleeding were similar between groups. Although the number of events was small, more intraocular bleeds occurred in the apixaban arm compared to warfarin (0.2% per year vs. 0.1% per year). Of note, apixaban was shown in pharmacology/toxicology studies to be detectable in the eye at 1 week even though plasma levels are not measurable after 24 hours. In looking at major bleeding according to baseline characteristics, the advantage of apixaban was maintained across most subgroups. Patients with a history of TIA/stroke, severe renal impairment, baseline aspirin use, and older patients experienced higher rates of major bleeding regardless of the assigned treatment arm, but the relative safety benefit of apixaban over warfarin remained.

In the AVERROES study, apixaban was associated with a similar risk of major bleeding and no excess of intracranial hemorrhage or gastrointestinal bleeding compared to aspirin in doses of 81-324 mg daily in patients with nonvalvular AF. Minor bleeding events were more frequent with apixaban vs. aspirin.

In the APPRAISE-2 study, the addition of full dose apixaban to the standard of care (aspirin plus a P2Y12-receptor antagonist, mainly clopidogrel) in an ACS population was stopped early because the increased risk of bleeding was not balanced with a reduction in ischemic events. Apixaban plus single antiplatelet therapy was associated with an annual major bleeding rate of 2.8% compared to 0.6% per year with single antiplatelet therapy alone. When apixaban was added to dual antiplatelet therapy, the annual bleeding rate was increased to 5.9% per year vs. 2.5% with dual antiplatelet therapy alone. Note that annual major bleeding rates with apixaban plus a single antiplatelet agent in APPRAISE-2 were similar to annual major bleeding rates with warfarin from ARISTOTLE (2.8% and 3.1%, respectively).

| Selected Bleeding Events From ARISTOTLE |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&n

| Major bleed | 327 (2.1) | 462 (3.1) | 0.69 (0.6-0.8) | <0.001 |
| Intracranial | 52 (0.3) | 122 (0.8) | 0.42 (0.3-0.58) | <0.001 |
| Gastrointestinal | 105 (0.8) | 119 (0.9) | 0.89 (0.7-1.15) | 0.37 |
| Intracutaneous | 32 (0.2) | 22 (0.1) | 1.42 (0.83-2.45) | - |
| Major or clinically relevant nonmajor bleed | 613 (4.1) | 877 (6) | 0.68 (0.61-0.75) | <0.001 |
Adverse events following discontinuation\textsuperscript{17}

Of the patients who completed the study treatment, 84% received an oral vitamin K antagonist (VKA) during the 30 days after the end of the study treatment period in ARISTOTLE. Patients that were transitioned off apixaban were about 4 times more likely to experience a primary endpoint event (mostly ischemic stroke) in the 30 days after stopping apixaban than patients in the warfarin treatment arm (21 events vs. 5 events; HR 4.07; 95% CI 1.54-10.81). Nearly all of the events occurred between days 3 and 30. In examining the patient characteristics, patients in the apixaban treatment arm experiencing a primary endpoint event in the 30 days after discontinuation had higher baseline CHADS2 scores and were more likely to have a history of TIA/stroke. INR data for patients was not available. A similar trend of excess events with apixaban was observed in patients who discontinued the study prematurely; however, the difference between apixaban and warfarin groups was not significantly different.

Similar findings have been reported in other pivotal trials and with other agents in the same drug class. In AVERROES, there was a higher rate of stroke and systemic embolism observed within the first 30 days following study discontinuation in apixaban treated patients who completed the study.\textsuperscript{17} Rivaroxaban, another factor Xa inhibitor, was associated with an almost 4-fold increased risk of stroke compared to warfarin in study completers in the pivotal ROCKET AF study.\textsuperscript{24}

Temporary Interruptions in Therapy\textsuperscript{17}

Because of the excess of primary outcome events identified when apixaban was permanently discontinued, further analysis describing outcomes in patients who had temporary interruptions in treatment is of interest and included in the FDA Medical Review. About one-third of patients had study drug interruptions of greater than 3 days’ duration. There was a trend of more primary outcome events in the apixaban arm both during the interruption in therapy and within the 30 days after resuming treatment, with about 1 more event per 100-patient years (approximately 5 vs. 4 events per 100-patient years). The FDA noted that these event rates were not importantly different from event rates in study completers during the 30 days following discontinuation of therapy.

Hepatotoxicity\textsuperscript{12,13,14,15,17}

Because of the severe hepatotoxicity associated with the direct thrombin inhibitor ximelagatran, the clinical development programs for the newer anticoagulants including apixaban have undergone intensive investigation for similar effects. Dabigatran and rivaroxaban were not associated with severe hepatotoxicity in clinical trials. Data for the hepatic safety of apixaban for FDA approval was based on information from the phase 3 ARISTOTLE and AVERROES trials. Proportions of patients experiencing transaminase elevations >3x ULN were generally balanced between groups or slightly lower with apixaban than the comparator of warfarin or aspirin. Potential Hy’s law cases, a more specific indicator of drug induced liver injury (aminotransferase [ALT] >3x upper limit of normal [ULN] plus total bilirubin >2x ULN), occurred infrequently with apixaban and its comparator, with no cases classified as “probably” related to study drug. The FDA also examined other liver related adverse events and discontinuations and concluded that the data do not suggest a risk of drug induced liver toxicity with apixaban.

Hypersensitivity\textsuperscript{8}

Hypersensitivity reactions have been reported in less than 1% of apixaban treated patients.

Tolerability\textsuperscript{12,14}

In ARISTOTLE, 7.6% of patients discontinued apixaban due to adverse events compared to 8.4% with warfarin. Overall discontinuation rates of study medication were significantly lower with apixaban compared to warfarin in ARISTOTLE (25.3% vs. 27.5% of total patients; p=0.001) and aspirin in AVERROES (17.9% per year vs. 20.5% per year; p=0.03).

For further details on the safety results of the clinical trials, refer to Appendix: Clinical Trials.

Contraindications\textsuperscript{8}

Apixaban is contraindicated in patients with active pathological bleeding and history of a severe hypersensitivity reaction to apixaban.
Boxed Warning

Increased risk of stroke upon discontinuation of apixaban
Patients are at increased risk of thrombotic events when apixaban is discontinued in the absence of alternative adequate anticoagulation. Increased rates of stroke were observed in clinical trials in patients with AF. If apixaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant. (See Safety/Other Adverse Events section for more information)

Other Warnings and Precautions

Patients with prosthetic heart valves
The safety and efficacy of apixaban has not been studied in patients with prosthetic heart valves. Therefore, per the manufacturer’s label, use of apixaban is not recommended.

Dabigatran, an oral direct thrombin inhibitor, is associated with an increased risk of adverse outcomes (e.g., valve thrombosis, stroke, myocardial infarction) in patients with mechanical prosthetic heart valves. Patients with prosthetic mechanical heart valves were excluded from the pivotal clinical trials with apixaban and rivaroxaban, the two Factor Xa inhibitors available in the US. Because of the known adverse outcomes with a related agent (dabigatran) and the lack of data available with apixaban and rivaroxaban, these agents should not be used in patients with prosthetic mechanical heart valves. Use of these agents in the setting of other forms of valvular disease, including the presence of a bioprosthetic valve, has not been specifically studied and not recommended by VA PBM.

Bleeding
As an anticoagulant, apixaban may cause serious or fatal bleeding (see Adverse Events/Safety section). Risk factors for bleeding include the co-administration of other medications that increase bleeding risk (e.g., antiplatelet agents, heparins, fibrinolytic therapy, other anticoagulants, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and chronic use of NSAIDs) and labor and delivery. Patients should be educated on signs and symptoms of blood loss and importance of prompt evaluation. Apixaban should be discontinued in the setting of acute, pathological bleeding.

There is no known reversal agent or antidote for apixaban, though the drug has a shorter duration of action compared to warfarin. Effects may persist for about 24 hours after the last dose. Based on the high protein binding, apixaban is not expected to be dialyzable. Studies conducted in healthy subjects suggest that activated charcoal may reduce the absorption of apixaban and may be considered in cases of suspected overdose.

There are no data and/or rationale to support the following: protamine, vitamin K, antifibrinolytics (e.g., tranexamic acid, aminocaproic acid), desmopressin or aprotinin. There are no clinical trials evaluating the use of prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa in patients who are bleeding.

In a randomized, double-blind, placebo-controlled cross-over study, a 4-factor PCC (at a dose of 50 IU/kg x 1) was shown to reverse the anticoagulant effects of rivaroxaban (another oral Xa inhibitor), as measured by laboratory assay (PT and endogenous thrombin potential) in 12 healthy volunteers. While these results using surrogate markers and healthy volunteers are promising, it is unknown whether or not PCC would be safe and effective in patients on apixaban with serious bleeding events. In addition, the effects of using another dose of PCC or a different PCC product (i.e., 3-factor product) have not been evaluated.

Though clinical data on the optimal management of bleeding with apixaban is lacking, general hemostatic measures should be employed:

- Discontinue treatment with apixaban and investigate the source of bleeding
- Implement supportive measures to control severe bleeding: delay further anticoagulant treatment, use mechanical compression or surgical hemostasis, consider transfusion of blood products (e.g., packed red cells or fresh frozen plasma)

Updated version may be found at www.pbm.va.gov or vaww.pbm.va.gov
Pregnancy and Lactation

Apixaban is a FDA Pregnancy Category B drug; no adequate or well-controlled studies have been conducted in pregnant women. Animal reproduction studies (rats, rabbits, and mice) did not reveal an increased risk for fetal malformations, toxicity, or maternal or fetal bleeding-related deaths; however, increased maternal bleeding was observed in all three species at varying exposures.

Treatment is likely to increase bleeding risk during pregnancy, labor, and delivery. Apixaban should be used in pregnant women only if the potential benefit justifies the potential risk to mother and fetus. Females of childbearing potential should discuss pregnancy planning with their physician.

It is unknown if apixaban is excreted in human milk. Apixaban was excreted in milk of rats (12% of maternal dose). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants exposed to apixaban, discontinue nursing or apixaban therapy, considering the importance of the drug vs. nursing to the mother.

Sentinel Events

None

Risk Evaluation and Mitigation Strategy (REMS)

As part of the REMS program for apixaban, a Dear Healthcare Professional Letter and a Dear Professional Organization letter are available to inform providers on: 1) the risks of thrombotic events in patients with nonvalvular AF when discontinuing apixaban without the use of an adequate alternative anticoagulant; and 2) the importance of following recommended instructions when converting from apixaban to other anticoagulants.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>First DataBank</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 2.5mg, 5mg tab</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Argatroban, Rivaroxaban</td>
</tr>
<tr>
<td>Eliquis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Eliphos, Eligard</td>
</tr>
</tbody>
</table>

Drug-Drug Interactions

Apixaban is a substrate of CYP3A4 and P-gp. Inhibitors of CYP3A4 and/or P-gp will increase apixaban exposure and potentially increase bleeding risk. Conversely, inducers of CYP3A4 and/or P-gp will reduce apixaban exposure and potentially increase the risk of stroke.

Based on in-vitro studies, apixaban is not expected to alter the clearance of drugs metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19.

Strong dual inhibitors of CYP3A4 and P-gp

The manufacturer recommends a dose reduction to 2.5 mg twice daily when apixaban is used concomitantly with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) based on pharmacokinetic studies demonstrating increased exposure. In patients taking the reduced apixaban dose of 2.5 mg twice daily due to patient characteristics (age ≥80 years, weight ≤60 kg, or SCr ≥1.5 mg/dL), the manufacturer recommends avoiding apixaban co-administration with strong dual inhibitors of CYP3A4 and P-gp.

Strong dual inducers of CYP3A4 and P-gp

Updated version may be found at www.pbm.va.gov or vawww.pbm.va.gov
The manufacturer recommends avoiding the use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) due to decreased apixaban exposure and potential reduced effectiveness.

**Pharmacodynamic Interactions**
The use of apixaban combined with medications that affect hemostasis is expected to increase the risk of bleeding (e.g., aspirin, anti-platelet agents, other antithrombotic agents, fibrinolytics, chronic NSAIDs).

Pharmacodynamic interaction studies conducted with aspirin, clopidogrel and the combination revealed no increase in Factor Xa activity when administered with apixaban. However, co-administration of apixaban with naproxen or enoxaparin increased anti-Factor Xa activity by 50-60%.

**Aspirin/Clopidogrel**
Concomitant aspirin use (at doses of ≤165 mg) in ARISTOTLE was associated with an increased risk of bleeding in both the apixaban groups and warfarin groups. Annual bleeding rates with apixaban increased from 1.8% to 3.4% and with warfarin from 2.7% to 4.6% when aspirin was also used.

Use of clopidogrel and clopidogrel plus aspirin was limited to only 2% of the ARISTOTLE population, so effects on bleeding could not be analyzed. In an ACS population, the addition of apixaban to the standard of care (aspirin plus P2Y12-receptor antagonist, mostly clopidogrel) was found to significantly increase bleeding risk in the APPRAISE-2 trial. The trial was stopped early due to the increased bleeding risk without an improvement in the risk of recurrent ischemic events.

**Drug-Lab Interactions**
Routine coagulation monitoring of apixaban is not required based on the stable pharmacokinetic and pharmacodynamic properties of the drug. Apixaban prolongs clotting tests including the prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT); however, the effects are highly variable. A specific assay to measure the effects of apixaban on factor Xa activity during the clinical development program was shown to produce concentration dependent increases in anti-Xa activity in both healthy patients and patients with AF.

The manufacturer does not recommend using these tests as a measure of effectiveness for apixaban.
References


Updated version may be found at www.pbm.va.gov or vaww.pbm.va.gov

**Appendix: Clinical Trials**

### Stroke Prevention in AF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Interventions/Endpoints</th>
<th>Baseline/Efficacy/Conclusions</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE (Granger et al)</td>
<td>Inclusion criteria: ≥18 yrs; permanent or persistent AF or flutter plus ≥1 of the following: ≥75 yrs; prior stroke, TIA, SE, sx HF in 3 mos or LVEF ≤40%; DM; HTN</td>
<td>Treatments: APIX 5 mg oral BID+ PBO (reduced dose of 2.5 mg oral BID given if ≥2 of the following at baseline: age ≥80 yrs; wt ≤60 kg; SCr ≥1.5 g/dL)</td>
<td>Baseline: median age 70 yr; 65% male; 43% VKA naive; 19% prior stroke, TIA, SE; mean CHADS2=2.1; mean TTR=62%; 31% baseline ASA; 4.7% APIX pts received reduced dose</td>
<td>Safety:</td>
</tr>
<tr>
<td>N=18,201</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MC, DB, RCT</td>
<td>Exclusion criteria: Reversible AF/flutter; clinically significant MS; increased bleeding risk considered a contraindication to oral anticoagulation; conditions other than AF that require anticoagulation (e.g., prosthetic mechanical heart valve); uncontrolled HTN (SBP &gt;180 mmHg or DBP &gt;100 mmHg); endocarditis; planned major sx; planned AF/flutter ablation procedure; ASA &gt;165 mg/d; ASA + thienopyridine; life expectancy &lt;1 yr; active EtOH/drug abuse; stroke within 7d; SCr &gt;2.5mg/dL or CrCl &lt;25 mL/min; AST or ALT &gt;2x ULN or total bil ≥1.5x ULN; plt ≤100K; Hgb &lt;9 g/dL; inability to comply with INR monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy:**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>APIX (n=9120)</th>
<th>WARF (n=9081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Endpt: stroke or SE*</td>
<td>n</td>
<td>%/yr</td>
</tr>
<tr>
<td>Ischemic stroke or uncertain type</td>
<td>212</td>
<td>1.27</td>
</tr>
<tr>
<td>Hemorrhagic stroke*</td>
<td>162</td>
<td>0.97</td>
</tr>
<tr>
<td>All-cause death*</td>
<td>603</td>
<td>3.52</td>
</tr>
<tr>
<td>Stroke, SE, any death*</td>
<td>752</td>
<td>4.49</td>
</tr>
<tr>
<td>MI</td>
<td>90</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*p <0.05 for between group difference

**Safety:**

- Any AE on tx 7406 (81.5) 7521 (83.1)
- Discontinuation due to AE 688 (7.6) 758 (8.4)
- Serious AE 3182 (35) 3302 (36.5)

**Discontinuations:** 25.3% APIX vs. 27.5% WARF pts stopped study drug before end of trial (p <0.05)

**Note:** Prespecified hierarchical sequential testing was conducted on 1) 1° endpoint for noninferiority; 2) 1° endpoint for superiority; 3) major bleeding; and lastly 4) any cause death.

**Summary/Conclusions:**
- APIX superior to WARF for reduction in stroke/SE, driven mainly by less hemorrhagic strokes
- No reduction in ischemic stroke with APIX vs. WARF
- Less major bleeding with APIX vs. WARF
- Increased risk of stroke in the 30 days following DC of APIX

**Event Rates 1-30d after permanent DC in study completers:**

<table>
<thead>
<tr>
<th>Total Events</th>
<th>APIX (n=6810)</th>
<th>WARF (n=6588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>n</td>
<td>%/yr</td>
</tr>
<tr>
<td>21</td>
<td>4.02</td>
<td>5</td>
</tr>
</tbody>
</table>

- LFT elevations were uncommon and similar b/t groups
- More strokes after permanent discontinuation of APIX in study completers
<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Interventions/Endpoints</th>
<th>Baseline/Efficacy/Conclusions</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERROES (Connolly et al)</td>
<td>Inclusion criteria: ≥50 yrs; permanent, persistent or paroxysmal AF plus ≥1 of the following: prior stroke/TIA, age ≥75 yrs, HTN on tx, DM, NYHA HF Class II or greater or LVEF ≤35% w/i 6 mos, or PAD; expected or documented to be unsuitable for VKA tx for 1 of following: DC for poor control, AE, interve ntions/Endpoints: VKA naïve; yr: 59% Baseline: AVERROES Safety: TIA, mean ASA 67% before (Connolly et al) or paroxysmal AF</td>
<td>Baseline: median age 70 yr; 59% male; 60% VKA naïve; 14% prior stroke, TIA, SE; mean CHADS2=2; 67% ASA before study; 6% APIX pts received reduced dose; 65% on study dose of 81 mg ASA Discontinuations: 17.9%/yr APIX vs. 20.5%/yr ASA (p &lt;0.05) Efficacy: <strong>1° Endpt:</strong> stroke or SE* <strong>2° Endpoints:</strong> MI, vascular death, all cause death, composite of vascular events Safety Endpoints: major (defined as clinically overt with death, involvement of critical site, fall in Hgb ≥2 g/dL, transfusion of ≥2 units) and nonmajor clinically relevant bleeding events</td>
<td>Safety: Major bleed 44 (1.4) Intradural bleed 11 (0.4) Nonmajor clinically relevant bleed 96 (3.1) GI bleed 12 (0.4) Minor* 188 (6.3)</td>
<td></td>
</tr>
<tr>
<td>MC, DB, RCT Superiority study</td>
<td>ASA 81-324 mg daily Note: Open label ASA was strongly discouraged when thienopyridines were not permitted. If pt developed indication for dual antiplatelet therapy, then pts allowed to continue study drug. Duration: Event-driven; stopped early d/t clear benefit Median l/f/u: 1.1 yrs</td>
<td><strong>1° Endpt:</strong> composite of stroke (ischemic, hemorrhagic or uncertain) and SE <strong>2° Endpoints:</strong> MI, vascular death, all cause death, composite of vascular events</td>
<td><strong>APIX (n=2808)</strong></td>
<td><strong>ASA (n=2791)</strong></td>
</tr>
<tr>
<td>ITT Multinational</td>
<td><strong>Endpoint</strong></td>
<td><strong>APIX (n=2808)</strong></td>
<td><strong>ASA (n=2791)</strong></td>
<td><strong>p&lt;0.05 for between group difference</strong></td>
</tr>
<tr>
<td>Supported by Bristol- Myers Squibb and Pfizer</td>
<td>Exclusion criteria: Reversible AF; valvular disease requiring sgx; planned ablation w/i 3 mos; conditions other than AF requiring anticoagulation; serious bleeding in past 6 mos or high bleed risk (e.g., PUD, plt &lt;100k, Hgb &lt;10 g/dL, stroke w/i 10d, bleeding tendency or dyscrasia); ETOH or drug abuse; SCr &gt;2.5 mg/dL or CrCl &lt;25 ml/min; ALT/AST &gt;2xULN; total bill ≥1.5x ULN; ASA allergy; females of childbearing potential who are pregnant, unwilling, or unable use acceptable contraception or meet pregnancy test requirements</td>
<td><strong>Stroke, MI, vascular death, major bleeding</strong> <em>p&lt;0.05 for between group difference</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE=adverse event; AF=atrial fibrillation; ASA=aspirin; AST=aspartate aminotransferase; ALT alanine aminotransferase; CrCl=creatinine clearance; CV=cardiovascular; DB=double-blind; DM=diabetes mellitus; DBP=diastolic blood pressure; DVT=deep vein thrombosis; ECG=electrocardiogram; ETOH=alcohol; GI=gastrointestinal; GI=gastrintestinal bleed; HF=heart failure; Hgb=hemoglobin; HTN=hypertension; INR=international normalized ratio; ITT=intent to treat; LFT=liver function test; LV=left ventricular; LVEF=left ventricular ejection fraction; MC=multicenter; MI=myocardial infarction; MS=mitral stenosis; N=number of pts with outcome/total pts; NSAIDs=non-steroidal anti-inflammatory drugs; NYHA=New York Heart Association; PAD=peripheral arterial disease; PBO=placebo; PC=placebo-controlled; PE=pulmonary embolism; pp=n=number of pts with outcome/total pts; RCT=randomized controlled trial; SBP=systolic blood pressure; SCr=serum creatinine; SE=systemic embolism; TIA=transient ischemic attack; TTR=time in therapeutic range; ULN=upper limit of normal; VKA=vitamin K antagonist; VTE=venous thromboembolism

Updated version may be found at www.pbm.va.gov or vaww.pbm.va.gov