APIXABAN- apixaban tablet, film coated
Amneal Pharmaceuticals of New York LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APIXABAN TABLETS safely and effectively. See full prescribing information for APIXABAN TABLETS.

APIXABAN tablets, for oral use
Initial U.S. Approval: 2012

WARNING: (A) PREMATURE DISCONTINUATION OF APIXABAN TABLETS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF APIXABAN TABLETS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including apixaban tablets, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if apixaban tablets are discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.4, 5.1, 14.1)
(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with apixaban tablets who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.3)

INDICATIONS AND USAGE

Apixaban tablets are a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

DOSAGE AND ADMINISTRATION

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.1)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg and 5 mg. (3)

CONTRAINDICATIONS

- Active pathological bleeding. (4)
- Severe hypersensitivity to apixaban. (4)

WARNINGS AND PRECAUTIONS

- Apixaban tablets can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms

of blood loss. An agent to reverse the anti-factor Xa activity of apixaban is available. (5.2)
- Prosthetic heart valves: Apixaban use not recommended. (5.4)
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: Apixaban use not recommended. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories, Inc. at 1-800-934-6729 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban. Reduce apixaban dose or avoid coadministration. (2.5, 7.1, 12.3)
- Simultaneous use of combined P-gp and strong CYP3A4 inducers reduces blood levels of apixaban: Avoid concomitant use. (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Not recommended. (8.1)
- *Lactation:* Discontinue drug or discontinue nursing. (8.2)
- *Severe Hepatic Impairment:* Not recommended. (8.7, 12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF APIXABAN TABLETS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF APIXABAN TABLETS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including apixaban tablets, increases the risk of thrombotic events. If anticoagulation with apixaban tablets is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4), Warnings and Precautions (5.1), and Clinical Studies (14.1)].*

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with apixaban tablets who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of apixaban tablets and neuraxial procedures is not known *[see Warnings and Precautions (5.3)]***

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

Apixaban tablets are indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Apixaban tablets are indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

Apixaban tablets are indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

Apixaban tablets are indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

Apixaban tablets are indicated to reduce the risk of recurrent DVT and PE following initial therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose of apixaban tablets for most patients is 5 mg taken orally twice daily.

The recommended dose of apixaban tablets is 2.5 mg twice daily in patients with at least two of the following characteristics:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of apixaban tablets is 2.5 mg taken orally 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 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of apixaban tablets is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of apixaban tablets is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE *[see Clinical Studies (14.3)]*.

2.2 Missed Dose

If a dose of apixaban tablets is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

2.3 Temporary Interruption for Surgery and Other Interventions

Apixaban tablets should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding *[see Warnings and Precautions (5.2)].* Apixaban tablets should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping apixaban tablets and prior to the intervention is not generally required. Apixaban tablets should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

2.4 Converting from or to Apixaban Tablets

Switching from warfarin to apixaban tablets: Warfarin should be discontinued and apixaban tablets started when the international normalized ratio (INR) is below 2.0.

Switching from apixaban tablets to warfarin: Apixaban tablets affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue apixaban tablets and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban tablets would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from apixaban tablets to anticoagulants other than warfarin (oral or parenteral): Discontinue apixaban tablets and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of apixaban tablets.

Switching from anticoagulants other than warfarin (oral or parenteral) to apixaban tablets: Discontinue the anticoagulant other than warfarin and begin taking apixaban tablets at the usual time of the next dose of the anticoagulant other than warfarin.

2.5 Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving apixaban tablets doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when apixaban tablets are co-administered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Clinical Pharmacology (12.3)]*.

In patients already taking 2.5 mg twice daily, avoid co-administration of apixaban tablets with combined P-gp and strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.

2.6 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg apixaban tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally *[see Clinical Pharmacology (12.3)]*. Alternatively, apixaban tablets may be crushed and suspended in 60 mL of

water or D5W and promptly delivered through a nasogastric tube *[see Clinical Pharmacology (12.3)]*.

Crushed apixaban tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg, yellow, round, biconvex, film-coated tablets debossed with “M” on one side and “2.5” on other side.
- 5 mg, pink, oval, biconvex, film-coated tablets debossed with “M” on one side and “5” on other side.

4 CONTRAINDICATIONS

Apixaban is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to apixaban (e.g., anaphylactic reactions) *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including apixaban, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from apixaban to warfarin in clinical trials in atrial fibrillation patients. If apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1)]*.

5.2 Bleeding

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue apixaban in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of apixaban is available. The pharmacodynamic effect of apixaban can be expected to persist for at least 24 hours

after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies *[see Clinical Pharmacology (12.2)]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage (10)]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of apixaban. The next dose of apixaban should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of apixaban for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.4 Patients with Prosthetic Heart Valves

The safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves. Therefore, use of apixaban is not recommended in these patients.

5.5 Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of apixaban is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

5.6 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including apixaban, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with

APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased Risk of Thrombotic Events After Premature Discontinuation *[see Warnings and Precautions (5.1)].*
- Bleeding *[see Warnings and Precautions (5.2)].*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions (5.3)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of apixaban was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14)]*, including 11,284 patients exposed to apixaban 5 mg twice daily and 602 patients exposed to apixaban 2.5 mg twice daily. The duration of apixaban exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with apixaban and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on apixaban and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

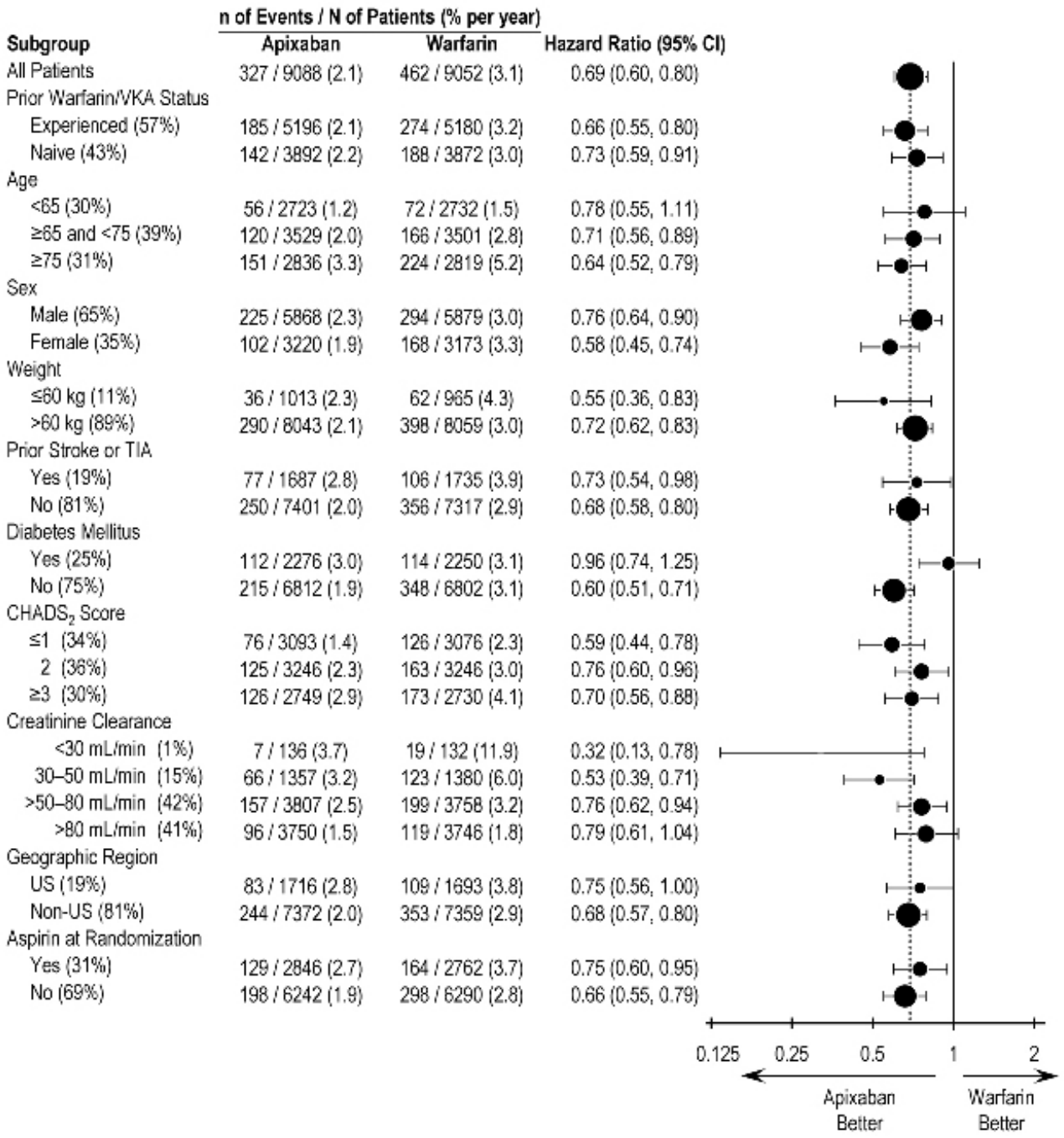
	Apixaban N=9088 n (per 100 pt-year)	**Warfarin N=9052 n (per 100 pt-year)**	**Hazard Ratio (95% CI)**	**P-value**
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001

Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3% per year) than did subjects without diabetes (1.9% per year).

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	Apixaban	Aspirin	Hazard Ratio	P-value

	N=2798 n (%/year)	N=2780 n (%/year)	(95% CI)	
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving apixaban.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of apixaban has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	Apixaban 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	Apixaban 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	Apixaban 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)

Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site[§]	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM[¶]	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

[*] All bleeding criteria included surgical site bleeding.
[†] Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
[‡] Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
[§] Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
[¶] CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	Apixaban, n (%) 2.5 mg po bid N=5924	**Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904**
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma, and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine	50 (0.8)	71 (1.2)

aminotransferase abnormal)		
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of apixaban has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to apixaban 10 mg twice daily, 3359 patients exposed to apixaban 5 mg twice daily, and 840 patients exposed to apixaban 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to apixaban was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) apixaban-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the apixaban-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, apixaban was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	Apixaban N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	Apixaban N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to apixaban was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) apixaban-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the apixaban-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	Apixaban 2.5 mg bid N=840 n (%)	Apixaban 5 mg bid N=811 n (%)	Placebo N=826 n (%)

Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	Apixaban 2.5 mg bid N=840 n (%)	**Apixaban 5 mg bid N=811 n (%)**	**Placebo N=826 n (%)**
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in apixaban-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

7 DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

7.1 Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving apixaban 5 mg or 10 mg twice daily, the dose of apixaban should be decreased by 50% when co-administered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

For patients receiving apixaban at a dose of 2.5 mg twice daily, avoid co-administration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with apixaban *[see Clinical Pharmacology (12.3)].*

7.2 Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of apixaban with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

7.3 Anticoagulants and Antiplatelet Agents

Co-administration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on apixaban from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with apixaban.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on apixaban use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reactions

Use of anticoagulants, including apixaban, may increase the risk of bleeding in the fetus and neonate.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Apixaban use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.3)]*.

Data

Animal Data

No developmental toxicities were observed when apixaban was administered during organogenesis to rats (orally), rabbits (intravenously) and mice (orally) at unbound apixaban exposure levels 4, 1, and 19 times, respectively, the human exposures at the MRHD. There was no evidence of fetal bleeding, although conceptus exposure was confirmed in rats and rabbits. Oral administration of apixaban to rat dams from gestation day 6 through lactation day 21 at maternal unbound apixaban exposures ranging from 1.4 to 5 times the human exposures at the MRHD was not associated with reduced maternal mortality or reduced conceptus/neonatal viability, although increased incidences of peri-vaginal bleeding were observed in dams at all doses. There was no evidence of neonatal bleeding.

8.2 Lactation

Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the

effects on the breastfed child, or the effects on milk production. Apixaban and/or its metabolites were present in the milk of rats *(see Data)*. Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with apixaban.

Data

Animal Data

Maximal plasma concentrations were observed after 30 minutes following a single oral administration of a 5 mg dose to lactating rats. Maximal milk concentrations were observed 6 hours after dosing. The milk to plasma AUC $_{(0\text{-}24)}$ ratio is 30:1 indicating that apixaban can accumulate in milk. The concentrations of apixaban in animal milk does not necessarily predict the concentration of drug in human milk.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including apixaban should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1)]*:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with apixaban did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent

hemodialysis, administration of apixaban at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1)]*. Clinical efficacy and safety studies with apixaban did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A).

Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with apixaban in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2)]*.

Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2)]*.

10 OVERDOSAGE

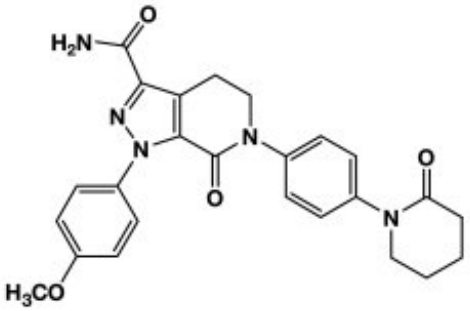
Overdose of apixaban tablets increases the risk of bleeding *[see Warnings and Precautions (5.2)]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

11 DESCRIPTION

Apixaban, a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

Apixaban tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, and iron oxide yellow (2.5 mg tablets) or iron oxide red (5 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

12.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of apixaban.

Effect of PCCs on Pharmacodynamics of Apixaban

There is no clinical experience to reverse bleeding with the use of 4-factor PCC products in individuals who have received apixaban.

Effects of 4-factor PCCs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels 4 hours after the initiation of a 30-minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued

to increase and exceeded pre-apixaban levels reaching a maximum (34%-51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21%-27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel *[see Warnings and Precautions (5.2)]*. A 50% to 60% increase in anti-FXa activity was observed when apixaban was co-administered with enoxaparin or naproxen.

Specific Populations

Renal impairment: Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology

Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

12.3 Pharmacokinetics

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of apixaban. Food does not affect the bioavailability of apixaban. Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of apixaban. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the C_{max} and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg apixaban tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Drug Interaction Studies

In *in vitro* apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

The effects of co-administered drugs on the pharmacokinetics of apixaban are summarized in Figure 2 *[see also Warnings and Precautions (5.2) and Drug Interactions (7)]*.

Figure 2: Effect of Co-administered Drugs on the Pharmacokinetics of Apixaban

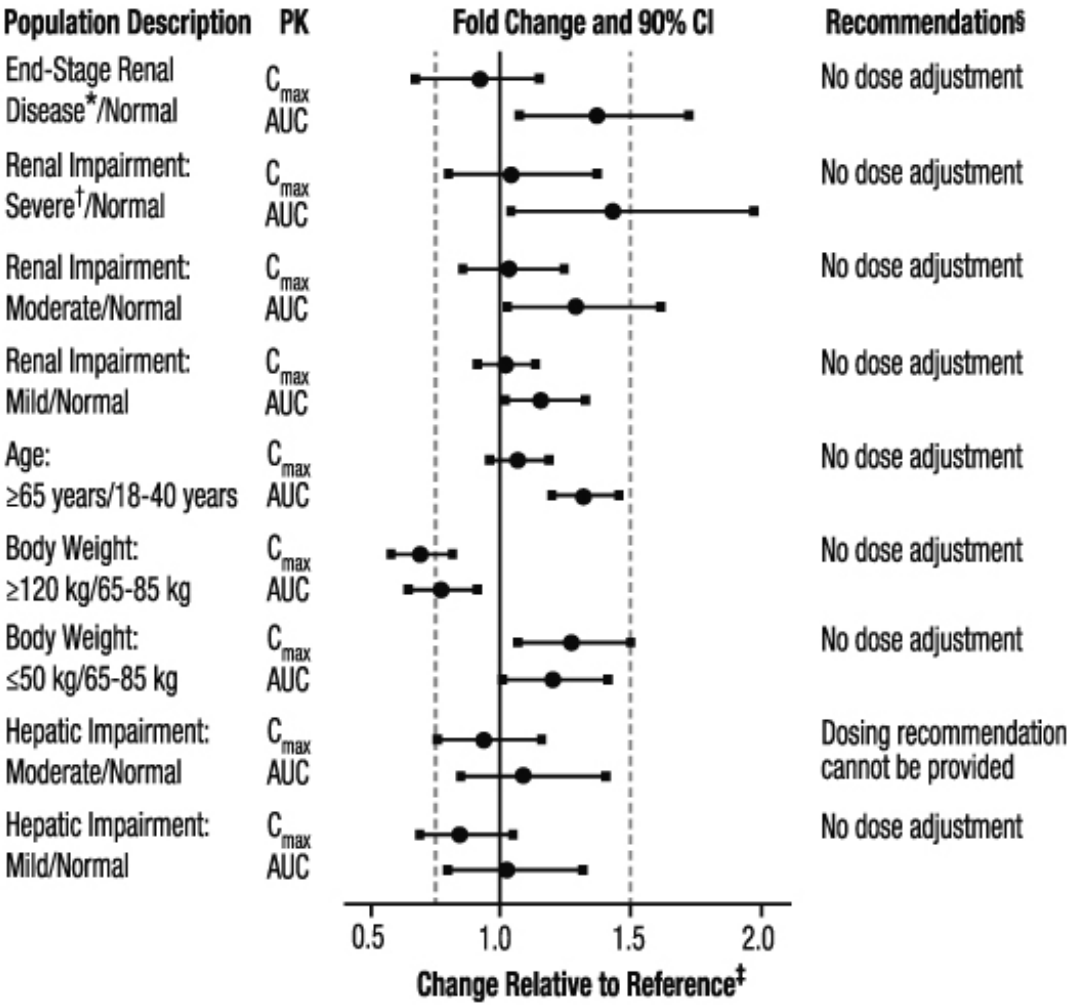
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of apixaban are summarized in Figure 3.

Figure 3: Effect of Specific Populations on the Pharmacokinetics of Apixaban



* ESRD subjects treated with intermittent hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.
† Results reflect CrCl of 15 mL/min based on regression analysis.
‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.
§ No dose adjustment is recommended for nonvalvular atrial fibrillation patients unless at least 2 of the following patient characteristics (age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL) are present.

Gender: A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

Race: The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function (Figure 3). The systemic exposure to apixaban administered 2

hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis.

Protein binding was similar (92%-94%) between healthy controls and ESRD subjects during the on-dialysis and off-dialysis periods.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Mutagenesis: Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Impairment of Fertility: Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in unbound apixaban exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F1-generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure to unbound apixaban that is 5 times the human exposure. Adverse effects in the F1-generation female offspring were limited to decreased mating and fertility indices at ≥200 mg/kg/day (a dose resulting in exposure to unbound apixaban that is ≥5 times the human exposure).

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ARISTOTLE

Evidence for the efficacy and safety of apixaban was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular AF comparing the effects of apixaban and warfarin on the risk of stroke and non-central nervous system (CNS) systemic embolism. In ARISTOTLE, patients were randomized to apixaban 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL) or to warfarin (targeted

to an INR range of 2.0 to 3.0). Patients had to have one or more of the following additional risk factors for stroke:

- prior stroke or transient ischemic attack (TIA)
- prior systemic embolism
- age greater than or equal to 75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether apixaban 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of apixaban to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) "naive," defined as having received ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0 to 3.0) of 62%.

Apixaban was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

Apixaban also showed significantly fewer major bleeds than warfarin *[see Adverse Reactions (6.1)]*.

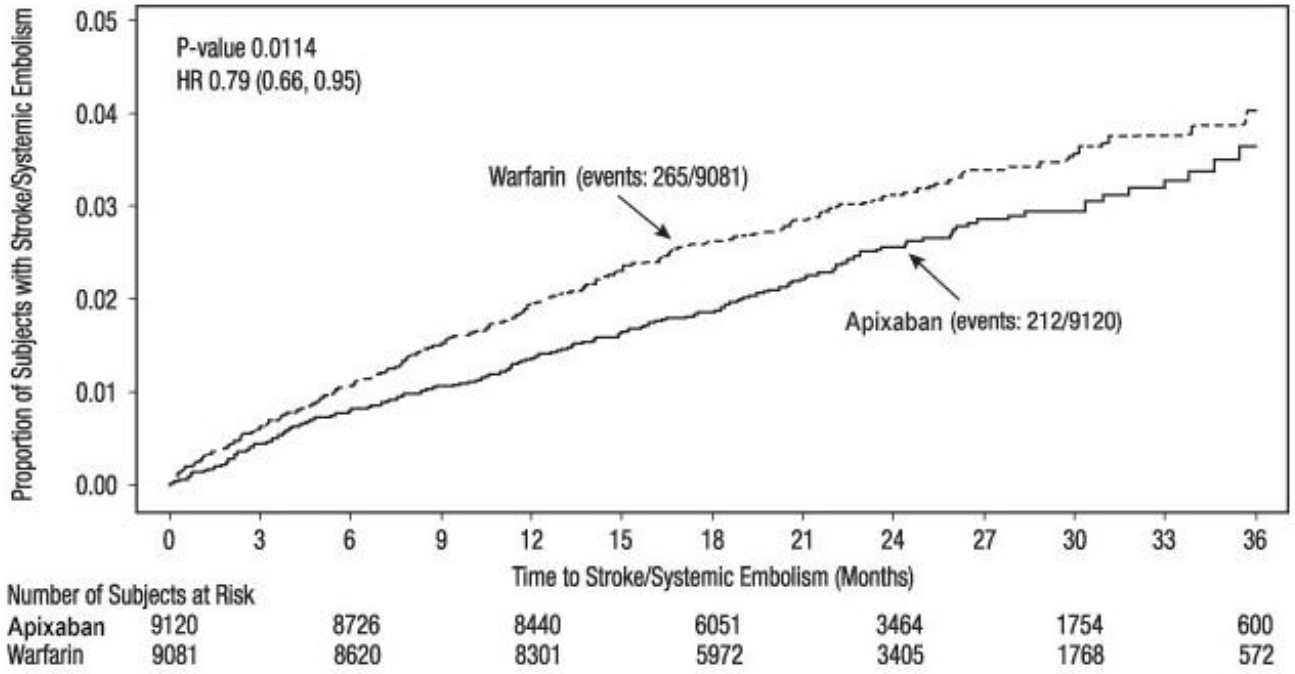
Table 9: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	Apixaban N=9120 n (%/year)	**Warfarin N=9081 n (%/year)**	**Hazard Ratio (95% CI)**	**P-value**
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
	40 (0.24)	78 (0.47)	0.51 (0.35	

Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

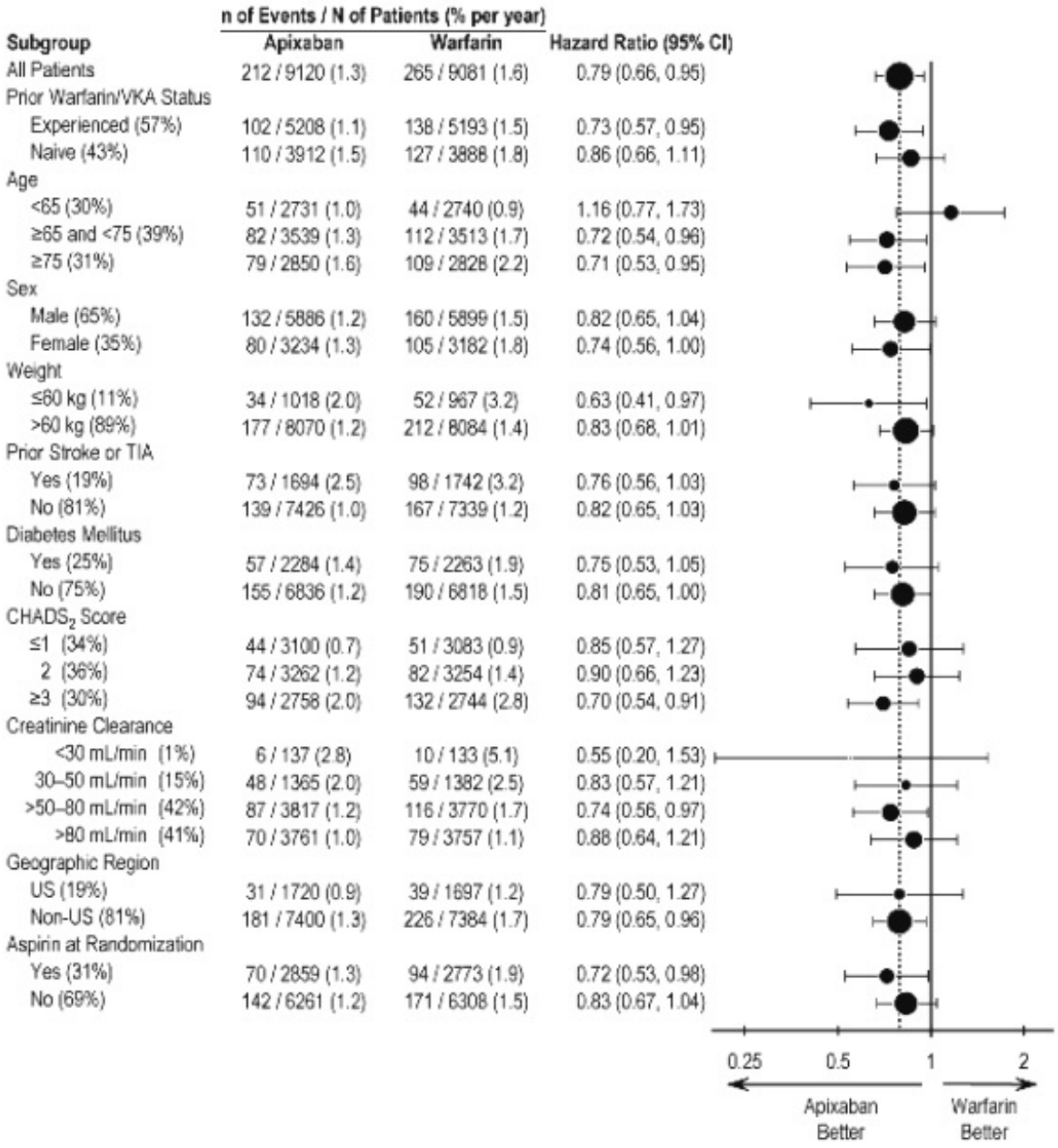
Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)



All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. Apixaban treatment resulted in a significantly lower rate of all-cause death ($p = 0.046$) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non vascular death rates were similar in the treatment arms.

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, $CHADS_2$ score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, and aspirin use at randomization (Figure 5).

Figure 5: Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

At the end of the ARISTOTLE study, warfarin patients who completed the study were generally maintained on a VKA with no interruption of anticoagulation. Apixaban patients who completed the study were generally switched to a VKA with a 2-day period of co-administration of apixaban and VKA, so that some patients may not have been adequately anticoagulated after stopping apixaban until attaining a stable and therapeutic INR. During the 30 days following the end of the study, there were 21 stroke or systemic embolism events in the 6791 patients (0.3%) in the apixaban arm compared

to 5 in the 6569 patients (0.1%) in the warfarin arm *[see Dosage and Administration (2.4)]*.

AVERROES

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if apixaban was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for apixaban compared to aspirin that was associated with a modest increase in major bleeding (Table 10) *[see Adverse Reactions (6.1)]*.

Table 10: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	Apixaban N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	-
Hemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	-
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	-
MI	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	-
All-cause death	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	-

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of apixaban is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥33 kg/m^2, and 625 patients with severe or moderate renal impairment.

In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either apixaban 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of apixaban was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, apixaban 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of apixaban was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the

ADVANCE-1 study, both apixaban and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period. In ADVANCE-3 and ADVANCE-2, the primary endpoint was tested for noninferiority, then superiority, of apixaban to enoxaparin. In ADVANCE-1, the primary endpoint was tested for noninferiority of apixaban to enoxaparin.

The efficacy data are provided in Tables 11 and 12.

Table 11: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	Apixaban 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
† Total VTE includes symptomatic and asymptomatic DVT and PE.
‡ Includes symptomatic and asymptomatic DVT.

Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			**ADVANCE-2**		
Events during 12-day treatment period	Apixaban 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	Apixaban 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value

Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE[†]/All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT[‡]	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT[‡]	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

[*] Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
[†] Total VTE includes symptomatic and asymptomatic DVT and PE.
[‡] Includes symptomatic and asymptomatic DVT.

The efficacy profile of apixaban was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).

14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

Efficacy and safety of apixaban for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following 6 to 12 months of anticoagulant treatment was derived from the AMPLIFY and AMPLIFY-EXT studies. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. All key safety and efficacy endpoints were adjudicated in a blinded manner by an independent committee.

AMPLIFY

The primary objective of AMPLIFY was to determine whether apixaban was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with apixaban 10 mg twice daily orally for 7 days followed by apixaban 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0 to 3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, an existing heart valve or atrial fibrillation, or active bleeding were excluded from the AMPLIFY study. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

A total of 5244 patients were evaluable for efficacy and were followed for a mean of 154 days in the apixaban group and 152 days in the enoxaparin/warfarin group. The mean age was 57 years. The AMPLIFY study population was 59% male, 83% Caucasian, 8% Asian, and 4% Black. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0 to 3.0) was 60.9%.

Approximately 90% of patients enrolled in AMPLIFY had an unprovoked DVT or PE at baseline. The remaining 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor in order to be randomized, which included previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

Apixaban was shown to be noninferior to enoxaparin/warfarin in the AMPLIFY study for the primary endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy (Table 13).

Table 13: Efficacy Results in the AMPLIFY Study

	Apixaban N=2609 N	**Enoxaparin/Warfarin N=2635 n**	**Relative Risk (95% CI)**
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

*Noninferior compared to enoxaparin/warfarin (P-value <0.0001).
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was consistent between the two subgroups.

AMPLIFY-EXT

Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulant therapy without having a recurrent event were randomized to treatment with apixaban 2.5 mg orally twice daily, apixaban 5 mg orally twice daily, or placebo for 12 months. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

A total of 2482 patients were randomized to study treatment and were followed for a mean of approximately 330 days in the apixaban group and 312 days in the placebo group. The mean age in the AMPLIFY-EXT study was 57 years. The study population was 57% male, 85% Caucasian, 5% Asian, and 3% Black.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study. In the AMPLIFY-EXT study, both doses of apixaban were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE), or all-cause death (Table 14).

Table 14: Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	Apixaban 2.5 mg bid N=840	**Apixaban 5 mg bid N=813**	**Placebo N=829**	**Apixaban 2.5 mg bid vs Placebo**	**Apixaban 5 mg bid vs Placebo**
	n (%)				
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

* Patients with more than one event are counted in multiple rows.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Apixaban tablets are available as listed in the table below.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
2.5 mg	Yellow, round,	Debossed with	Bottles of 60	0115-

	biconvex	“M” on one side and “2.5” on the other side	Bottles of 1000 Hospital Unit-Dose Blister Package of 100	1721-13 0115-1721-03 0115-1721-01
5 mg	Pink, oval, biconvex	Debossed with “M” on one side and “5” on the other side	Bottles of 60 Bottles of 1000 Hospital Unit-Dose Blister Package of 100	0115-1722-13 0115-1722-03 0115-1722-01

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue apixaban tablets without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with apixaban tablets. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking apixaban tablets, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions (5.3)]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with apixaban tablets *[see Use in Specific Populations (8.1, 8.2)]*.
- How to take apixaban tablets if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6)]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2)].*

Manufactured by:
MSN Laboratories Private Limited
Telangana 509216

India

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

1966-05

Rev. 5/2024

MEDICATION GUIDE

Apixaban (a pix’ a ban) **Tablets**

What is the most important information I should know about apixaban tablets?

- **For people taking apixaban tablets for atrial fibrillation:**

  People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. Apixaban tablets lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking apixaban tablets, you may have increased risk of forming a clot in your blood.

  Do not stop taking apixaban tablets without talking to the doctor who prescribes it for you. Stopping apixaban tablets increases your risk of having a stroke.

  Apixaban tablets may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed apixaban tablets for you when you should stop taking it. Your doctor will tell you when you may start taking apixaban tablets again after your surgery or procedure. If you have to stop taking apixaban tablets, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- **Apixaban tablets can cause bleeding** which can be serious and rarely may lead to death. This is because apixaban tablets are a blood thinner medicine that reduces blood clotting.

  You may have a higher risk of bleeding if you take apixaban tablets and take other medicines that increase your risk of bleeding, including:
  - aspirin or aspirin-containing products
  - long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (COUMADIN®, JANTOVEN®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to help prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

While taking apixaban tablets:
- you may bruise more easily
- it may take longer than usual for any bleeding to stop

Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking apixaban tablets:

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

- **Apixaban tablets are not for patients with artificial heart valves.**
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like apixaban tablets, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

If you take apixaban tablets and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.
- Apixaban tablets are not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing, who have a history of blood clots.

What are apixaban tablets?

Apixaban tablets are a prescription medicine used to:
- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

It is not known if apixaban tablets are safe and effective in children.

Who should not take apixaban tablets?

Do not take apixaban tablets if you:
- currently have certain types of abnormal bleeding.
- have had a serious allergic reaction to apixaban tablets. Ask your doctor if you are not sure.

What should I tell my doctor before taking apixaban tablets?

Before you take apixaban tablets, tell your doctor if you:
- have kidney or liver problems
- have antiphospholipid syndrome
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if apixaban tablets will harm your unborn baby.
- **Females who are able to become pregnant:** Talk with your healthcare provider about pregnancy planning during treatment with apixaban tablets. Talk with your healthcare provider about your risk of severe uterine bleeding if you are treated with blood thinner medicines, including apixaban tablets.
- are breastfeeding or plan to breastfeed. It is not known if apixaban passes into your breast milk. You and your doctor should decide if you will take apixaban tablets or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking apixaban tablets. They should talk to the doctor who prescribed apixaban tablets for you, before you have **any** surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way apixaban tablets works. Certain medicines may increase your risk of bleeding or stroke when taken with apixaban tablets. See "**What is the most important information I should know about apixaban tablets?**"

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take apixaban tablets?
- **Take apixaban tablets exactly as prescribed by your doctor.**
- Take apixaban tablets twice every day with or without food.
- Do not change your dose or stop taking apixaban tablets unless your doctor tells you to.
- If you miss a dose of apixaban tablets, take it as soon as you remember. Do not take more than one dose of apixaban tablets at the same time to make up for a missed dose.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take apixaban tablets.
- Your doctor will decide how long you should take apixaban tablets. **Do not stop taking it without first talking with your doctor. If you are taking apixaban tablets for atrial fibrillation, stopping apixaban tablets may increase your**

risk of having a stroke.
- **Do not run out of apixaban tablets. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have apixaban tablets available to avoid missing any doses.
- If you take too much apixaban tablets, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

What are the possible side effects of apixaban tablets?
- See "**What is the most important information I should know about apixaban tablets?**"
- Apixaban tablets can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of apixaban tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store apixaban tablets?

Store apixaban tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep apixaban and all medicines out of the reach of children.

General Information about Apixaban Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use apixaban tablets for a condition for which it was not prescribed. Do not give apixaban tablets to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about apixaban tablets that is written for health professionals.

For more information, call Impax Laboratories, Inc. at 1-800-934-6729 or go to www.impaxlabs.com.

What are the ingredients in apixaban tablets?

Active ingredient: apixaban.

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, and iron oxide yellow (2.5 mg tablets) or iron oxide red (5 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
MSN Laboratories Private Limited
Telangana 509216
India

Distributed by:

Amneal Pharmaceuticals LLC

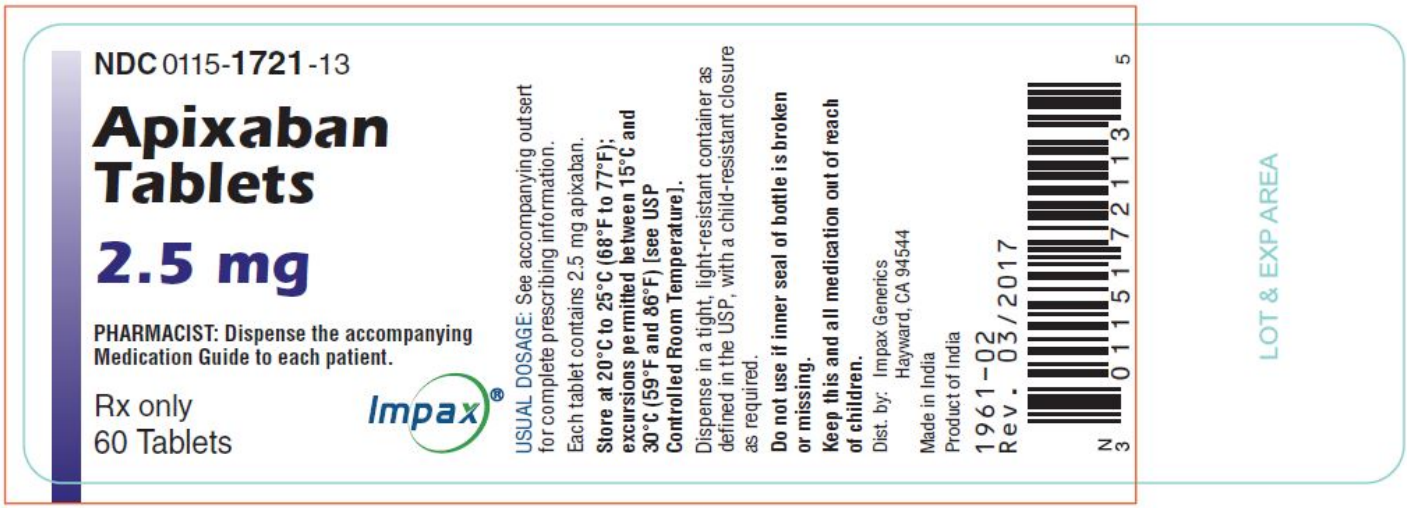
Bridgewater, NJ 08807

1967-05

Rev. 5/2024

Principal Display Panel

NDC 0115-1721-13
2.5 mg, 60 Tablets



Principal Display Panel

NDC 0115-1722-13
5 mg, 60 Tablet

APIXABAN

apixaban tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1721
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
APIXABAN (UNII: 3Z9Y7UWC1J) (APIXABAN - UNII:3Z9Y7UWC1J)	APIXABAN	2.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics			
Color	yellow	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	M;2;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1721-13	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/31/2018	
2	NDC:0115-1721-03	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/31/2018	
3	NDC:0115-1721-01	10 in 1 CARTON	08/31/2018	
3	NDC:0115-1721-15	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209810	08/31/2018	

APIXABAN

apixaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1722
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
APIXABAN (UNII: 3Z9Y7UWC1J) (APIXABAN - UNII:3Z9Y7UWC1J)	APIXABAN	5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	pink	**Score**	no score
Shape	OVAL	**Size**	10mm

Flavor		**Imprint Code**	M;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1722-13	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/31/2018	
2	NDC:0115-1722-03	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/31/2018	
3	NDC:0115-1722-01	10 in 1 CARTON	08/31/2018	
3	NDC:0115-1722-15	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209810	08/31/2018	

Labeler - Amneal Pharmaceuticals of New York LLC (123797875)

Revised: 5/2024 Amneal Pharmaceuticals of New York LLC