Summary of Product Characteristics for Pharmaceutical Products

1. Name of the Medicinal Product

APIXARED 5MG TABLET

2. Qualitative And Quantitative Composition

Each film-coated tablet contains 5 mg of Apixaban.

Excipient with potential clinical effect:

Each film-coated tablet contains Lactose

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Film-coated tablet

Pink colored, oval shaped, biconvex, film coated tablet, debossed with '5' on one side and plain on the other side.

4. Clinical Particulars

4.1 Indications:

1. Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

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

2. Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Apixaban is 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.

3. Treatment of Deep Vein Thrombosis Apixaban is indicated for the treatment of DVT.

4.Treatment of Pulmonary Embolism Apixaban is indicated for the treatment of PE.

5.Reduction in the Risk of Recurrence of DVT and PE

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

4.2 Posology and Administration:

Posology

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

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

The recommended dose of Apixaban 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 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 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 is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.

Missed dose

If a dose of Apixaban 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.

Temporary Interruption for Surgery and Other Interventions

Apixaban 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. Apixaban 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 and prior to the intervention is not generally required. Apixaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Converting from or to Apixaban

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

Switching from Apixaban to warfarin: Apixaban 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 and begin both a parenteral anticoagulant and warfarin at the time the next dose of Apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

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

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

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving Apixaban doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when Apixaban is coadministered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, itraconazole, ritonavir).

In patients already taking 2.5 mg twice daily, avoid coadministration of Apixaban with combined P-gp and strong CYP3A4 inhibitors

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. Alternatively, Apixaban tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube.

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

4.3 Contraindications:

Apixaban is contraindicated in patients with the following conditions:

- Active pathological bleeding
- Severe hypersensitivity reaction to Apixaban (e.g., anaphylactic reactions)

4.4 Special warnings and precautions for use

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.

Bleeding

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

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 antiinflammatory drugs (NSAIDs).

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. 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.

Hemodialysis does not appear to have a substantial impact on apixaban exposure. 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.

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.

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.

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.

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 2glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

4.5 Interaction with other medicinal products

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.

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 coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir).

For patients receiving Apixaban at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors.

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.

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.

Anticoagulants and Antiplatelet Agents

Coadministration 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.

4.6. Fertility, Pregnancy and Lactation

Pregnancy

Risk Summary

The limited available data on Apixaban use in pregnant women are insufficient to inform drugassociated 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.

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.

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. Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with Apixaban.

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 (0-24) 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.

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.

4.7. Effects on Ability to Drive and Use Machines

Apixaban has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects

The following clinically significant adverse reactions are discussed in greater detail in other sections.

- Increased Risk of Thrombotic Events After Premature Discontinuation
- Bleeding
- Spinal/Epidural Anesthesia or Puncture

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, 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	**Warfarin**	**Hazard Ratio**	**P-value**
	N=9088 n (per 100 pt-year)	**N=9052 n (per 100 pt-year)**	**(95% CI)**	
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.

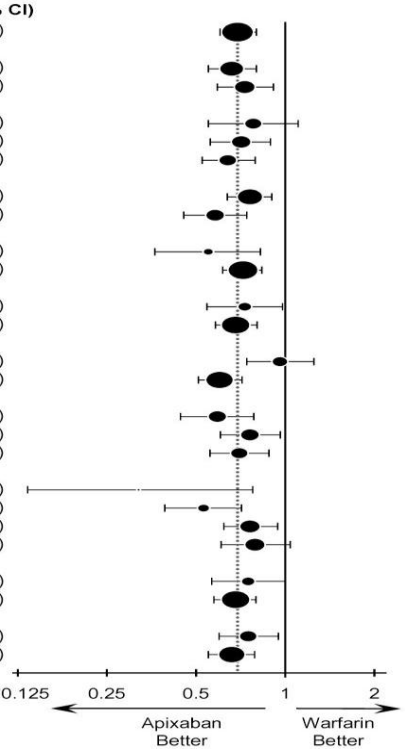
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** 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, CHADS2 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

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30–50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50–80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



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=2780**	**(95% CI)**	
	n (%/year)	**n (%/year)**		

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	First dose	First dose	First dose	First dose	First dose
	12 to 24	9 to 15	12 to 24	9 to 15	12 to 24	12 to 24
	hours post	hours prior	hours post	hours prior	hours post	hours post
	surgery	to surgery	surgery	to surgery	surgery	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 reoperation 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 aminotransferase abnormal)	50 (0.8)	71 (1.2)
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

	Apixaba n N=2676	**Enoxaparin/Warfari n N=2689**	**Relative Risk (95% CI)**
	n (%)	**n (%)**	
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	**Enoxaparin/Warfari n**
	N=2676	**N=2689**
	n (%)	**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	**Apixaban 5 mg bid N=811**	**Placebo N=826**
	n (%)	**n (%)**	**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	**Apixaban 5 mg bid**	**Placebo**
	N=840	**N=811**	**N=826**
	n (%)	**n (%)**	**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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board-Pharmacovigilance Electronic Reporting System (PvERS); https://pv.pharmacyboardkenya.org .

4.9 Overdose

Overdose of Apixaban increases the risk of bleeding.
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF02
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.
Pharmacodynamic effects:
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. A 50% to 60% increase in anti-FXa activity was observed when Apixaban was coadministered 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.

5.2 Pharmacokinetic properties

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 (Cmax) 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 Cmax 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.

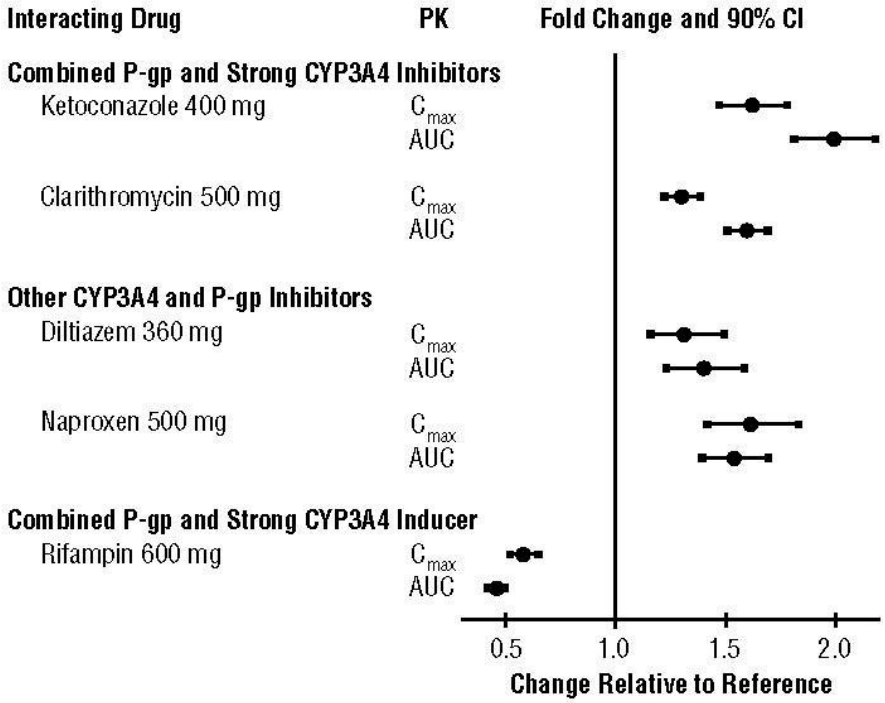
Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

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 coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

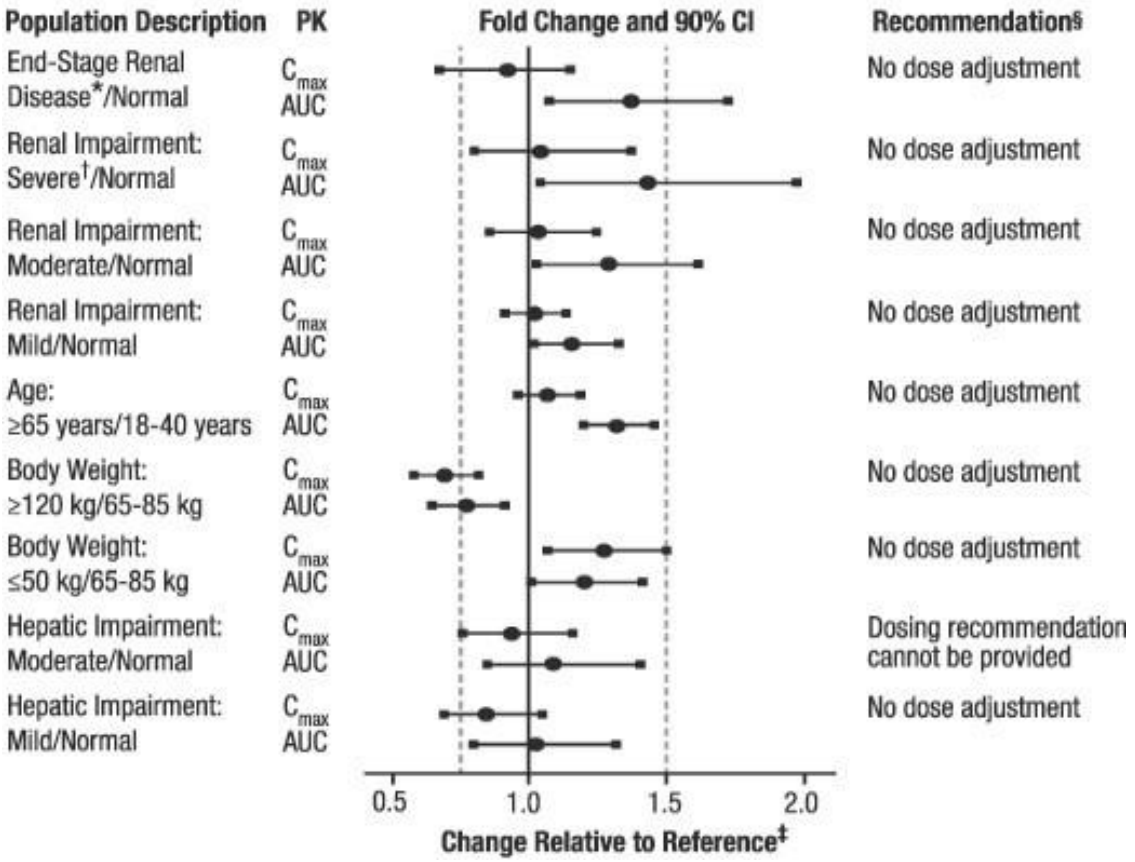
The effects of coadministered drugs on the pharmacokinetics of apixaban are summarized in Figure 2

Figure 2: Effect of Coadministered 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.

5.3 Pre-Clinical Safety Data

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).

6. Pharmaceutical Particulars

6.1 List of Excipients

Tablet core:

Lactose Anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Sodium lauryl sulfate
Magnesium stearate
Purified water

Film coat:

Opadry Pink 32K540165 includes:
HPMC 2910/Hypromellose
Lactose Monohydrate
Titanium Dioxide
Triacetin
Iron Oxide Red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store below 30^0C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container Primary packaging:

Pack size: Blister pack
Primary packing materials:
- Forming foil: PVC/PVdC Film Clear 188mm/0.25mm (90 GSM)
- Lidding foil: Hard Tempered Alu Plain Foil 25 MICRON W:252mm) NC Free

Secondary packing materials: Carton

6.6 Special Precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Dr. Reddy's Laboratories Limited,
8-2-337, ROAD NO 3, BANJARA HILLS, HYDERABAD 500 034, INDIA.

8. Marketing Authorization Number(s)

H2025/CTD12543/27047

9. Date of First Authorization/Renewal of the Authorization

2025 May 22

10. Date Of Revision of the Text

2025 May 22