Andorivaban
2.5 mg Film coated tablets
10 mgFilm coated tablets
15 mgFilm coated tablets
20 mgFilm coated tablets
(Rivaroxaban)

▼**This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 6 for how to report adverse reactions.**

WARNING:

(A) PREMATURE DISCONTINUATION OF ANDORIVABAN INCREASES THE RISK OF THROMBOTIC EVENTS,

(B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of ANDORIVABAN increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including ANDORIVABAN, increases the risk of thrombotic events. If anticoagulation with ANDORIVABAN is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with ANDORIVABAN 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 non-steroidal 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 ANDORIVABAN and neuraxial procedures is not known**
- **Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.**
- **Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis .**

1-INDICATIONS AND USAGE

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

ANDORIVABAN is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
There are limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.

1.2 Treatment of Deep Vein Thrombosis
ANDORIVABAN is indicated for the treatment of deep vein thrombosis (DVT).

1.3 Treatment of Pulmonary Embolism
ANDORIVABAN is indicated for the treatment of pulmonary embolism (PE).

1.4 Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism
ANDORIVABAN is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

1.5 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
ANDORIVABAN is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

1.6 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
ANDORIVABAN is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding [see Warnings and Precautions

1.7 Reduction of Risk of Major Cardiovascular Events in Patients with Chronic Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD)
ANDORIVABAN , in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

2-Dosage and Administration:

2.1 Recommended Dosage:
Table 1: Recommended Dosage

Indication	Renal Considerations*	Dosage	Food/Timing†
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation	CrCl>50 mL/min	20 mg once daily	Take with evening meal
	CrCl ≤50 mL/min§	15 mg once daily	Take with evening meal

Treatment of DVT and/or PE	CrCl ≥15 mL/min§	15 mg twice daily ▼ after 21 days, transition to ▼ 20 mg once daily	Take with food, at the same time each day
	CrCl<15 mL/min	Avoid Use	
Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE	CrCl ≥15 mL/min§	10 mg once daily, after at least 6 months of standard anticoagulant treatment	Take with or without food
	CrCl<15 mL/min	Avoid Use	
Prophylaxis of DVT Following:			
-Hip Replacement Surgery‡	CrCl ≥15 mL/min§	10 mg once daily for 35 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl<15 mL/min	Avoid Use	
-Knee Replacement Surgery‡	CrCl ≥15 mL/min§	10 mg once daily for 12 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl<15 mL/min	Avoid Use	
Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding	CrCl ≥15 mL/min§	10 mg once daily, in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days	Take with or without food
	CrCl<15 mL/min	Avoid Use	
Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in Chronic CAD or PAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75100 mg) once daily	Take with or without food

* Calculate CrCl based on actual weight. See Warnings and Precautions and Use in Specific Populations
† See Clinical Pharmacology
‡ See Dosage and Administration
§ Patients with CrCl<30 mL/min were not studied, but administration of rivaroxaban is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) [see Use in Specific Populations]

2.2 Switching to and from ANDORIVABAN

Switching from Warfarin to ANDORIVABAN -When switching patients from warfarin to ANDORIVABAN , discontinue warfarin and start ANDORIVABAN as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

Switching from ANDORIVABAN to Warfarin -No clinical trial data are available to guide converting patients from ANDORIVABAN to warfarin. ANDORIVABAN affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue ANDORIVABAN and begin both a parenteral anticoagulant and warfarin at the time the next dose of ANDORIVABAN would have been taken.

Switching from ANDORIVABAN to Anticoagulants other than Warfarin -For patients currently taking ANDORIVABAN and transitioning to an anticoagulant with rapid onset, discontinue ANDORIVABAN and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next ANDORIVABAN dose would have been taken [see Drug Interactions (8.4)].

Switching from Anticoagulants other than Warfarin to ANDORIVABAN -For patients currently receiving an anticoagulant other than warfarin, start ANDORIVABAN 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start ANDORIVABAN at the same time.

2.3 Discontinuation for Surgery and other Interventions

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, ANDORIVABAN should be stopped at least 24 hours before the procedure to reduce the risk of bleeding *[see Warnings and Precautions (6.2)]*. In deciding whether a procedure should be delayed until 24 hours after the last dose of ANDORIVABAN , the increased risk of bleeding should be weighed against the urgency of intervention. ANDORIVABAN should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short *[see Warnings and Precautions (6.1)]*. If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.

2.4 Missed Dose

For patients receiving 2.5 mg twice daily: if a dose is missed, the patient should take a single 2.5 mg ANDORIVABAN dose as recommended at the next scheduled time

• For patients receiving 15 mg twice daily: The patient should take ANDORIVABAN immediately to ensure intake of 30 mg ANDORIVABAN per day. Two 15 mg tablets may be taken at once

. • For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed ANDORIVABAN dose immediately. The dose should not be doubled within the same day to make up for a missed dose

.

3. DOSAGE FORMS AND STRENGTHS

- 2.5mg film coated tablets.
- 10 mg film coated tablets.
- 15 mg film coated tablets.
- 20 mg film coated tablets.

4-Contra-indications:

ANDORIVABAN is contraindicated in patients with:

- active pathological bleeding (see Warnings and Precautions)
- severe hypersensitivity reaction to ANDORIVABAN (e.g., anaphylactic reactions) [see Adverse Reactions (7.2)]

5-Warnings and Precautions:

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ANDORIVABAN , in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ANDORIVABAN to warfarin in clinical trials in atrial fibrillation patients. If ANDORIVABAN 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].

5.2 Risk of Bleeding

ANDORIVABAN increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe ANDORIVABAN to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue ANDORIVABAN in patients with active pathological hemorrhage. The terminal elimination half-life of Rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.
Concomitant use of drugs that are known combined P-gp and strong CYP3A inhibitors increases Rivaroxaban exposure and may increase bleeding risk

Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding

Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of ANDORIVABAN for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (i.e. undergoing acute, in-hospital cancer treatment), active gastroduodenal ulcer in the three months prior to treatment, history of bleeding in the three months prior to treatment, or dual antiplatelet therapy. ANDORIVABAN is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable [see Clinical Pharmacology). Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant 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

To reduce the potential risk of bleeding associated with the concurrent use of ANDORIVABAN and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of ANDORIVABAN . Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of ANDORIVABAN is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of ANDORIVABAN [see Clinical Pharmacology)The next ANDORIVABAN dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of ANDORIVABAN for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), and bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly [see Dosage and Administration]. Consider dose adjustment or discontinuation of ANDORIVABAN in patients who develop acute renal failure while on ANDORIVABAN [see Use in Specific Populations].

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

In patients with CrCl<30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl<15 mL/min (including patients on dialysis); therefore, avoid the use of ANDORIVABAN in these patients.
Discontinue ANDORIVABAN in patients who develop acute renal failure while on treatment [see Use in Specific Populations].

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
In patients with CrCl<30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl<15 mL/min (including patients on dialysis); therefore, avoid the use of ANDORIVABAN in these patients.
Discontinue ANDORIVABAN in patients who develop acute renal failure while on treatment [see Use in Specific Populations].

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
In patients with CrCl<30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl<15 mL/min (including patients on dialysis); therefore, avoid the use of ANDORIVABAN in these patients.
Discontinue ANDORIVABAN in patients who develop acute renal failure while on treatment *[see Use in Specific Populations]*.

5.5Use in Patients with Hepatic Impairment
No clinical data are available for patients with severe hepatic impairment.
Avoid use of ANDORIVABAN in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

5.6 Use with P-gp and Strong CYP3A Inhibitors or Inducers
Avoid concomitant use of ANDORIVABAN with known combined P-gp and strong CYP3A inhibitors *[see Drug Interactions]*.
Avoid concomitant use of ANDORIVABAN with drugs that are known combined P-gp and strong CYP3A inducers *[see Drug Interactions]*.

5.7 Risk of Pregnancy-Related Hemorrhage
In pregnant women, ANDORIVABAN should be used only if the potential benefit justifies the potential risk to the mother and fetus. ANDORIVABAN dosing in pregnancy has not been studied. The anticoagulant effect of ANDORIVABAN cannot be monitored with standard laboratory testing. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop

in hemoglobin and/or hematocrit, hypotension, or fetal distress) *[see Warnings and Precautions) and Use in Specific Populations]*.

5.8 Patients with Prosthetic Heart Valves

On the basis of the GALILEO study, use of ANDORIVABAN is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to ANDORIVABAN experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of ANDORIVABAN have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of ANDORIVABAN is not recommended in patients with prosthetic heart valves..

5.9 Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ANDORIVABAN is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

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

Direct-acting oral anticoagulants (DOACs), including ANDORIVABAN , 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.

Andorivaban contains lactose :

Patients with rare hereditary problems of galactose intolerance , the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine

6-Undesirable effects

The following clinically significant adverse reactions are also discussed in other sections of the labeling:

- Increased Risk of Stroke After Discontinuation in Nonvalvular Atrial Fibrillation *[see Warning and Warnings and Precautions*
- Bleeding Risk *[see Warnings and Precautions)]*
- Spinal/Epidural Hematoma *[see Boxed Warning and Warnings and Precautions]*

Clinical trials Experience:

Hemorrhage: The most common adverse reactions with Rivaroxaban were bleeding complications

Other Non-hemorrhagic **Adverse Reactions* Reported by ≥1% of** RIVAROXABAN **-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies:**

Gastrointestinal disorders
General disorders and administration site conditions
Fatigue
Musculoskeletal and connective tissue disorders
Back pain
Muscle spasm
Nervous system disorders
Dizziness
Psychiatric disorders
Anxiety
Depression
Insomnia
Skin and subcutaneous tissue disorders
Pruritus

Other Adverse Drug Reactions* Reported by ≥1% of RIVAROXABAN -Treated Patients in RECORD 1-3 Studies

Injury, poisoning and procedural complications
Wound secretion
Musculoskeletal and connective tissue disorders
Pain in extremity
Muscle spasm
Nervous system disorders
Syncope
Skin and subcutaneous tissue disorders
Pruritus
Blister

- Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia.

Gastrointestinal disorders: retroperitoneal hemorrhage.

Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury).

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema.

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS).

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows constant monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

Reporting side effects:

Egyptian Pharmacovigilance center (EPVC), EDA: pv.report@edaegypt.gov.eg

7- Drug Interactions

7.1 General Inhibition and Induction Properties

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

7.2 Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A Inhibitors

Avoid concomitant administration of Rivaroxaban with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions and Clinical Pharmacology]*.

Although clarithromycin is a combined P-gp and strong CYP3A inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with Rivaroxaban as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology)]*.

Interaction with Combined P-gp and Moderate CYP3A Inhibitors in Patients with Renal Impairment

Rivaroxaban should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions and Clinical Pharmacology]*.

7.3 Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems

Avoid concomitant use of Rivaroxaban with drugs that are combined P-gp and strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautionsand Clinical Pharmacology]*.

7.4 Anticoagulants and NSAIDs/Aspirin

Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding *[see Clinical Pharmacology]*.

Avoid concurrent use of Rivaroxaban with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions)]*.

8- USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on Rivaroxaban in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use Rivaroxaban with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery. The anticoagulant effect of Rivaroxaban cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of ANDORIVABAN for the mother and possible risks to the fetus when prescribing ANDORIVABAN to a pregnant woman *[see Warnings and Precautions]*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions

Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Labor or Delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery *[see Warnings and Precautions]*. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of ANDORIVABAN in this setting.

Data

Human Data

There are no adequate or well-controlled studies of rivaroxaban in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an *in vitro* placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

8.2 Lactation

Risk Summary

Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for rivaroxaban and any potential adverse effects on the breastfed infant from rivaroxaban or from the underlying maternal condition *(see Data)*.

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

. In clinical trials the efficacy of Rivaroxaban in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients

8.6 Renal Impairment

In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed

8.7 Hepatic Impairment

In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).
The safety or PK of rivaroxaban in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology]*.
Avoid the use of rivaroxaban in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

9- OVERDOSAGE

Overdose of ANDORIVABAN may lead to hemorrhage. Discontinue ANDORIVABAN and initiate appropriate therapy if bleeding complications associated with overdosage occur. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of ANDORIVABAN overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable [see Warnings and Precautions (6.2) and Clinical Pharmacology (10.3)]. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

10- Clinical Pharmacology:

10.1 Mechanism of Action

Rivaroxaban is a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

10.2 Pharmacodynamics

Dose-dependent inhibition of FXa activity was observed in humans. Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are also prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban.

Specific Populations

Renal Impairment

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in subjects with renal impairment relative to healthy control subjects *[see Use in Specific Populations (9)]*.

Table 10: Percentage Increase in Rivaroxaban PK and PD Measures in Subjects with Renal Impairment Relative to Healthy Subjects from

Studies

Measure	Parameter	Creatinine Clearance (mL/min)				
		50-79	30-49	15-29	ESRD (on dialysis)*	ESRD (post-dialysis)*
Exposure	AUC	44	52	64	47	56
FXa Inhibition	AUEC	50	86	100	49	33
PT Prolongation	AUEC	33	116	144	112	158

**Separate stand-alone study.*

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve

Hepatic Impairment

Anti-Factor Xa activity was similar in subjects with normal hepatic function and in mild hepatic impairment (Child-Pugh A class). There is no clear understanding of the impact of hepatic impairment beyond this degree on the coagulation cascade and its relationship to efficacy and safety.

10.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is dose-dependent. For the 2.5 mg and 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food. For the 20 mg dose in the fasted state, the absolute bioavailability is approximately 66%. Coadministration of Rivaroxaban with food increases the bioavailability of the 20 mg dose (mean AUC and Cmax increasing by 39% and 76% respectively with food). Rivaroxaban 15 mg and 20 mg tablets should be taken with food *[see Dosage and Administration)]*.

The maximum concentrations (Cmax) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH.Coadministration of Rivaroxaban (30 mg single dose) with the H2-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or Rivaroxaban (20 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban (see Figure 4).

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and Cmax compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban distal to the stomach which can result in reduced absorption and related drug exposure.

In a study with 44 healthy subjects, both mean AUC and Cmax values for 20 mg rivaroxaban administered orally as a crushed tablet mixed in applesauce were comparable to that after the whole tablet. However, for the crushed tablet suspended in water and administered via an NG tube followed by a liquid meal, only mean AUC was comparable to that after the whole tablet, and Cmax was 18% lower.

Distribution

Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

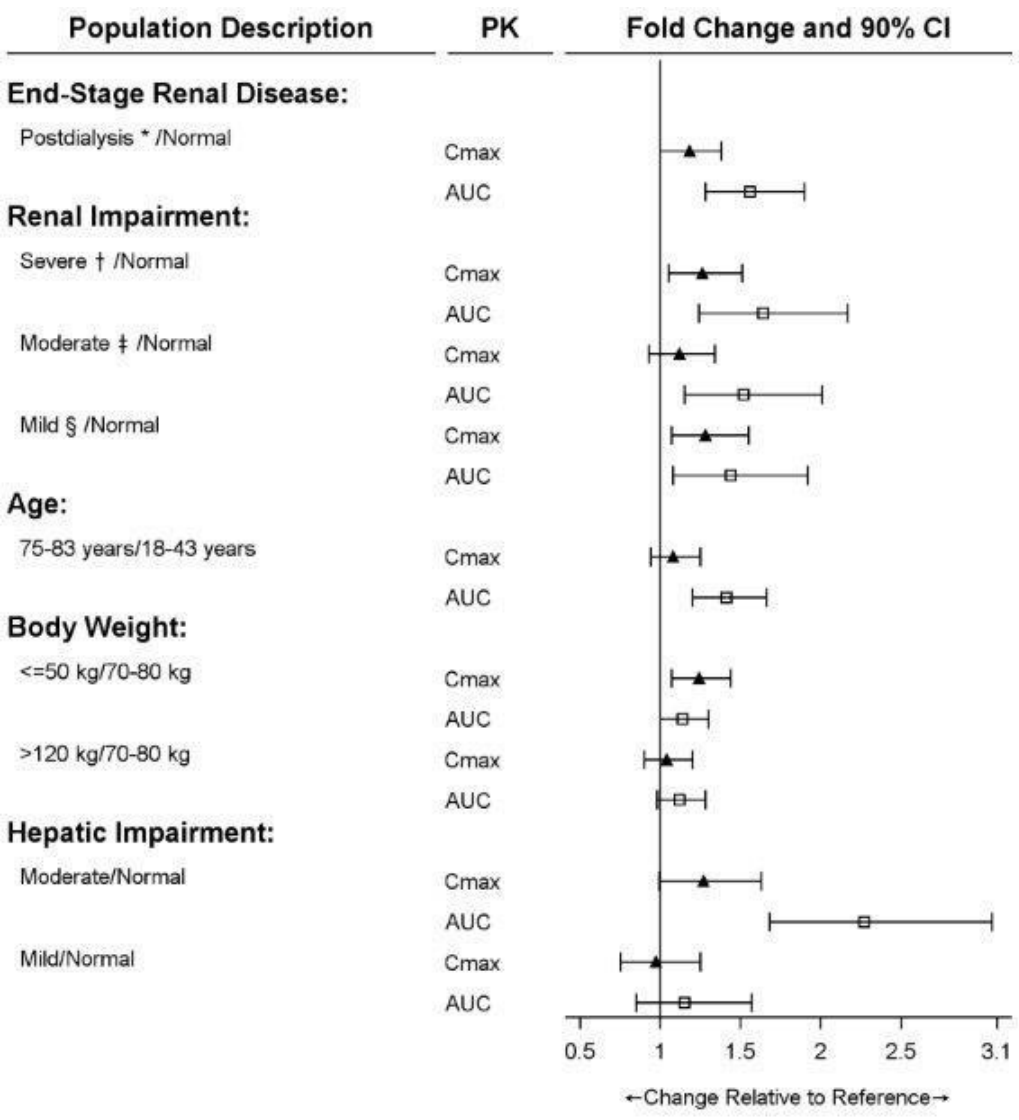
Excretion

In a Phase 1 study, following the administration of [^{14}C]-rivaroxaban, approximately one-third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Specific Populations

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



* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of rivaroxaban post hemodialysis.
† Creatinine clearance 15 to 29 mL/min.
‡ Creatinine clearance 30 to 49 mL/min.
§ Creatinine clearance 50 to 79 mL/min.

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of Rivaroxaban.

Race

Healthy Japanese subjects were found to have 20 to 40% on average higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly

The terminal elimination half-life is 11 to 13 hours in the elderly subjects aged 60 to 76 years *[see Use in Specific Populations]*.

Renal Impairment

The safety and pharmacokinetics of single-dose rivaroxaban (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Figure 3). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations]*.

Hemodialysis in ESRD subjects: Systemic exposure to rivaroxaban administered as a single 15 mg dose in ESRD subjects dosed 3 hours after the completion of a 4-hour hemodialysis session (post-dialysis) is 56% higher when compared to subjects with normal renal function (see Table 10). The systemic exposure to rivaroxaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 600 mL/min and a blood flow rate in the range of 320 to 400 mL/min is 47% higher compared to those with normal renal function. The extent of the increase is similar to the increase in patients with CrCl 15 to 50 mL/min taking Rivaroxaban 15 mg. Hemodialysis had no significant impact on rivaroxaban exposure. Protein binding was similar (86% to 89%) in healthy controls and ESRD subjects in this study.

Hepatic Impairment

The safety and pharmacokinetics of single-dose Rivaroxaban (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment. No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B). Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations]*.

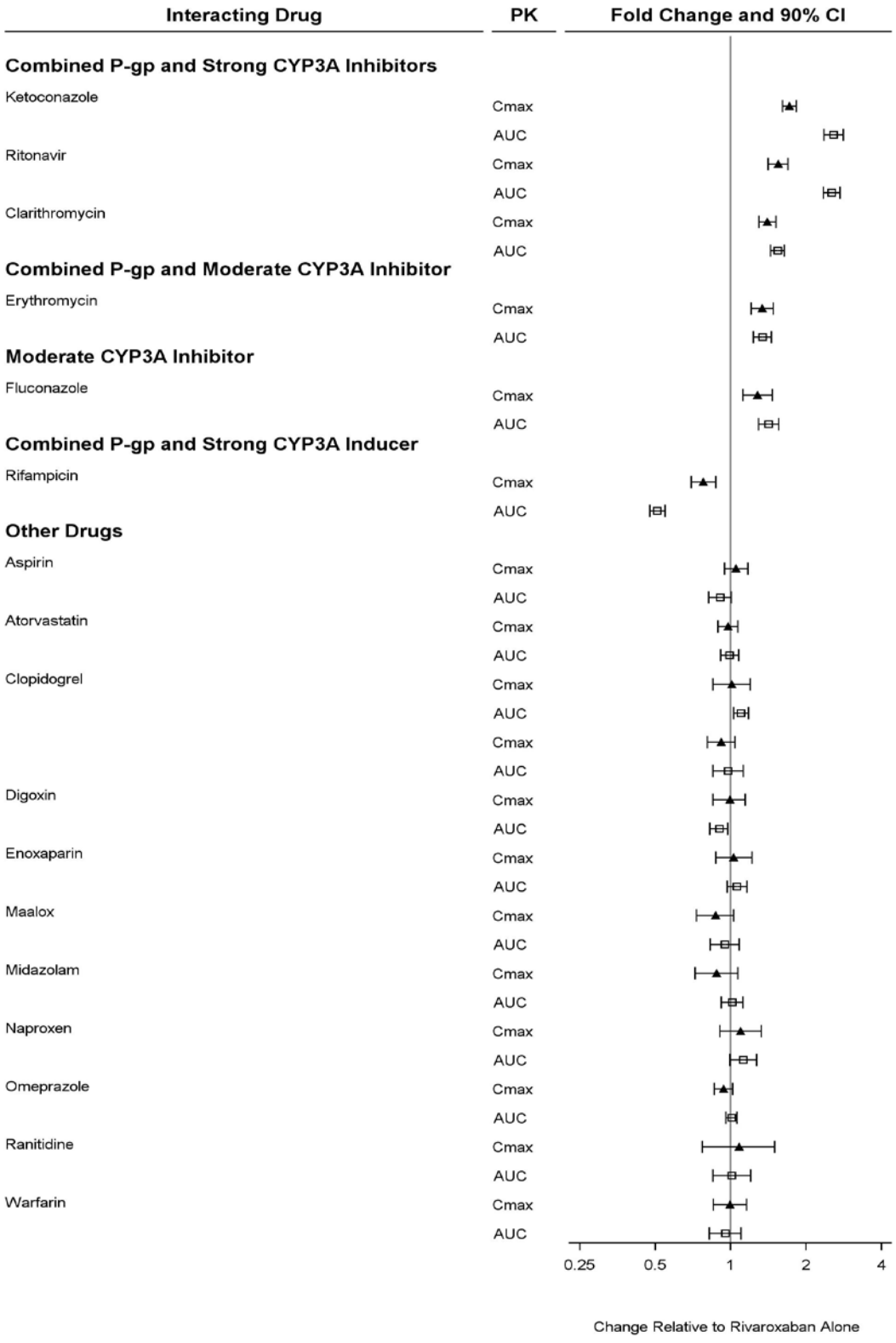
Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A nor induces CYP1A2, 2B6, 2C19, or 3A. In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

The effects of coadministered drugs on the pharmacokinetics of rivaroxaban exposure are summarized in Figure 4 [see Drug Interactions].

Figure 4: Effect of Coadministered Drugs on the Pharmacokinetics of Rivaroxaban

Anticoagulants



In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and Rivaroxaban (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. In another study, single doses of warfarin (15 mg) and Rivaroxaban (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Neither enoxaparin nor warfarin affected the pharmacokinetics of rivaroxaban

NSAIDs/Aspirin
In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with Rivaroxaban. Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban

Clopidogrel
In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and Rivaroxaban(15 mg single dose) were coadministered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems
In a pharmacokinetic trial, Rivaroxaban was administered as a single dose in subjects with mild (CrCl = 50 to 79 mL/min) or moderate renal impairment (CrCl = 30 to 49 mL/min) receiving multiple doses of erythromycin (a combined P-gp and moderate CYP3A inhibitor). Compared to Rivaroxaban administered alone in subjects with normal renal function (CrCl >80 mL/min), subjects with mild and moderate renal impairment concomitantly receiving erythromycin reported a 76% and 99% increase in AUCinf and a 56% and 64% increase in Cmax, respectively. Similar trends in pharmacodynamic effects were also observed.

11.6 QT/QTc Prolongation
In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for Rivaroxaban(15 mg and 45 mg, single-dose).

12. HOW SUPPLIED/STORAGE AND HANDLING

PACK

- **Andorivaban 2.5,15 &20 mg**

Carton box containing 1, 2 or3 (Al/transparent PVC/PVDC) strip of 10 film coated tablets and insert leaflet.

- **Andorivaban 10 mg**

Carton box containing 2 (Al/transparent (PVC/PVDC)) strips, each of 10 film coated tablets and insert leaflet.

STORAGE

- Store at a temperature not exceed 30 ^{o}C& in a dry place.
- Keep all medicines out of reach of children.

3. COMPOSITION

- The active ingredients of andorivaban are : rivaroxaban 2.5 mg ,10mg,15 mg & 20 mg
- The inactive ingredients of ANDORIVABAN are:
  Lactose monohydrate, hydroxypropyl methyl cellulose E5, croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose pH 101, talc powder (only for 2.5, 10 mg)- magnesium stearte.

- Additionally, the proprietary film coating used
  For ANDORIVABAN 2.5 mg is hydroxypropyl methyl cellulose E5, polyethylene glycol 6000, titanium dioxide, iron oxide yellow

  For ANDORIVABAN 10 mg tablets consist of hypromellose E5 , polyethylene glycol 6000 , titanium dioxide , iron oxide red

  For ANDORIVABAN 15 mg tablets is aquarius preferred HSP BPP 310130 Pink (hydroxypropyl methyl cellulose ,copovidone ,medium chain triglycerides ,polyethylene glycol,polydextrose titianium dioxide (CI 77891) ,carmoisine lake (CI 14720:1) & RED IRON OXIDE (CI 177491) "

  For ANDORIVABAN 20 mg tablets is Opadry green II (85f21781)

14. SHELF LIFE:
2 years

Manufactured by Al Andalous for Pharmaceutical Industries