File Information	Artwork Type [PLEASE TICK ✓]	Sign / Stamp
Product : T VAREXA FC TABLET [Front] SAP No. : - Version : RAS/V4 Date : 22 July 2023	☐ Unit Box ☑ Leaflet ☐ Aluminium Foil ☐ Outer Box ☐ Fix-A-Form ☐ Sachet ☐ Label ☐ Others : _____	

Document Category [PLEASE TICK ✓]	Pharmacode / QR Code / Others
☑ RA Submission Artwork ☐ NPRA Approval Copy ☐ Approval Copy Artwork ☐ Internal Artwork Circulation ☐ Previous Approved Artwork ☐ Draft Artwork ☐ Others : _____	

Remarks	Colour
Font : Times New Roman Regular (Spacing - 7.5pt / Size - 7.5pt) Dimension : 297mm(w) x 420mm(h)	Black 100% Colours shown on this proof are to indicate correct colour separations.

POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY

Prevention of VTE (VTEp): elective hip or knee replacement surgery

The recommended dose of Varexa is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

In patients undergoing hip replacement surgery: The recommended duration of treatment is 32 to 38 days

In patients undergoing knee replacement surgery: The recommended duration of treatment is 10 to 14 days

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)

The recommended dose of Varexa is 5 mg taken orally twice daily.

Dose reduction

The recommended dose of Varexa is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics; age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥1.5mg/dL (133 micromole/L).

Therapy should be continued long-term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)

The recommended dose of Varexa for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of Varexa for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 12 below-:

Table 12: Dose recommendation (VTEt)

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment f or DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

Missed dose

If a dose is missed, the patient should take Varexa immediately and then continue with twice daily intake as before.

Switching

Switching treatment from parenteral anticoagulants to Varexa (and vice versa) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to Varexa

When converting patients from vitamin K antagonist (VKA) therapy to Varexa, warfarin or other VKA therapy should be discontinued and Varexa started when the international normalised ration (INR) is < 2.

Switching from Varexa to VKA therapy

When converting patients from Varexa to VKA therapy, administration of Varexa should be continued for at least 2 days after beginning VKA therapy. After 2 days of co-administration of Varexa with VKA therapy, an INR should be obtained prior to the next scheduled dose of Varexa. Co-administration of Varexa and VKA therapy should be continued until the INR is ≥2.0.

Elderly

VTEp and VTEt – No dose adjustment required.

NVAF – No dose adjustment required, unless criteria for dose reduction are met.

Renal Impairment

In patients with mild or moderate renal impairment, the following recommendations apply:

- For the prevention of VTE in elective hip or knee replacement surgery (VTEp) – for apixaban 2.5 mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary.
- For the prevention of stroke and systemic embolism in patients with NVAF; and serum creatinine ≥1.5mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60kg, a dose reduction is necessary and described above. In absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary.

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply:

- For the prevention of VTE in elective hip or knee replacement surgery (VTEp) – for apixaban 2.5 mg, for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution
- For the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily.

In patients with creatinine clearance <15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, apixaban is not recommended.

Hepatic impairment

Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment.

Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical studies. Therefore Varexa should be used with caution in this population. Prior to initiating Varexa, liver function testing should be performed.

Body weight

VTEp and VTEt – No dose adjustment is required.

NVAF – No dose adjustment required, unless criteria for dose reduction are met.

Gender

No dose adjustment required.

Patients undergoing catheter ablation (NVAF)

Patients can continue apixaban while undergoing catheter ablation.

Patients undergoing cardioversion

Apixaban can be initiated or continued in NVAF patients who may require cardioversion.

For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image guided approach (i.e., transoesophageal echocardiography (TEE) or computed tomographic scan (CT)) prior to cardioversion should be considered, in accordance with the established medical guidelines.

For patients initiating treatment with apixaban, 5mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation. The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 single doses) if the patient meets the criteria for dose reduction.

If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patients meet the criteria for dose reduction. The administration of the loading dose should be given at least 2 hours before cardioversion.

For all patients undergoing cardioversion, confirmation should be sought prior to cardioversion that the patients have taken apixaban as prescribed. Decision on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)

There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after haemostasis is achieved.

Paediatric population

The safety and efficacy of Varexa in children and adolescents below age 18 have not been established. No data are available.

Method of administration

Oral use

Varexa should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Varexa tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Varexa tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube.

Crushed Varexa tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the excipients listed
- Active clinically significant bleeding
- Hepatic diseases associated with coagulopathy and clinically relevant bleeding risk
- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysm or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent, i.e., unfractionated heparin (UFH), low molecular weight heparin (enoxaparin, dalteparin, etc.), heparin derivatives (fondaprinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage risk

As with other anticoagulants, patients taking apixaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Apixaban administration should be discontinued if severe haemorrhage occurs.

Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.

Interaction with other medicinal products affecting haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulant is contraindicated. The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding.

Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non- steroidal anti-inflammatory medicinal products (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban.

In patients with atrial fibrillation and condition that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risk should be made before combining this therapy with apixaban.

In a clinical study of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical study, there was limited (2.1%) use of concomitant dual antiplatelet therapy.

A clinical study enrolled patients with atrial fibrillation with ACS and/or undergoing PCI and a planned treatment period with a P2Y12 inhibitor, with or without ASA, and oral anticoagulant (either apixaban or VKA) for 6 months. Concomitant use of ASA increased the risk of ISTH (International Society on Thrombosis and Hemostasis) major or CRNM (Clinically Relevant Non-Major) bleeding in apixaban-treated subjects from 16.4% per year to 33.1% per year.

In a clinical study of high-risk post-acute coronary syndrome patients without atrial fibrillation, characterised by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).

Use of thrombolytic agents for the treatment of acute ischemic stroke

There is limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered apixaban.

Patients with prosthetic heart valves

Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulant (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In general, for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2-glycoprotein I antibodies), treatment with DOACs should be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Surgery and invasive procedures

Apixaban should be discontinued -:

- At least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This include interventions for which the probability of clinically significant bleeding cannot be executed or for which the risk of bleeding would be unacceptable.
- At least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This include interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedure cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted.

Temporary discontinuation

Discontinuing anticoagulants, including Apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with Apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) 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 haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post- operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Apixaban. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, 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.

There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 hours (i.e., 2 x half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter removal. As with all new anticoagulant medicinal products, experience with neuraxial blockade is limited and extreme caution is therefore, recommended when using apixaban in the presence of neuraxial blockade.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Apixaban is not recommended as an alternative to unfractionated heparin in patients with heparin pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established in these clinical situations.

Patients with active cancer

Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risk should be made.

Patients with renal impairment

Apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15 -29 mL/min) which may lead to an increased bleeding risk. For the prevention VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 -29 mL/min).

For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29mL/min), and patients with serum creatinine ≥1.5mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60kg should receive the lower dose of apixaban 2.5mg twice daily.

In patients with creatinine clearance <15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, apixaban is not recommended.

Elderly patients

Increasing age may increase haemorrhagic risk. Also the co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Body weight

Low body weight (<60kg) may increase haemorrhagic risk.

Patients with hepatic impairment

Apixaban is contraindicated in patients with hepatic diseases associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment.

It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B).

Patients with elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical studies. Therefore, apixaban should be used cautiously in this population. Prior to initiating Varexa, liver function testing should be performed.

Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (i.e., ketoconazole, itraconazole, voriconazole, and posaconazole) and HIV protease inhibitors (i.e., ritonavir). These medicinal products may increase apixaban exposure by2-fold or greater in the presence of additional factors that increase apixaban exposure (i.e., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers (i.e., rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's Wort) may lead to a ~ 50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with co-administration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply -:

- For the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;
- For the treatment of DVT and treatment of PE, apixaban should not be used, since efficacy may be compromised

Hip fracture surgery

Apixaban has not been studied in clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, it is not recommended in these patients.

Laboratory parameters

Clotting test [i.e., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability.

Information about excipients
Varexa contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS
Inhibitors of CYP3A4 and P-gp
Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban Cmax.

The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (i.e., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (i.e., ritonavir).

Active substance which are not considered strong inhibitors of both CYP3A4 and P-gp, (i.e., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for apixaban is required when co-administered with agents that are not strong inhibitors of both CYP3A4 and P-gp. For example, diltiazem (360 mg once a day), considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in Cmax. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and Cmax, respectively. Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and Cmax respectively.

Inducers of CYP3A4 and P-gp
Co-administration of apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and Cmax, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (i.e., phenytoin, carbamazepine, phenobarbital, or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such medicinal products, however, in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE.

Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers both CYP3A4 and P-gp since efficacy may be compromised.

Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.

After combined administration of enoxaparin (40 mg single dose) with apixaban (5mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co- administered with ASA 325mg once a day.

Apixaban co-administered with clopidogrel (75mg once a day), or with combination of clopidogrel 75mg and ASA 162mg once daily, or with prasugrel (60mg followed by 10mg once daily) in Phase I studies did not show relevant increase in template bleeding time or further inhibition of platelet aggregation, compared to administration of the antiplatelet agents without apixaban. Increases in clotting test (PT, INR, and aPTT) were consistent with the effect of apixaban alone.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and Cmax, respectively. Corresponding increases in clotting tests were observed for apixaban. No change was observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are co-administered with apixaban. Apixaban should be used with caution when co-administered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk.
There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran, or sulfinpyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended.

Other concomitant therapies
No significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two medicinal products
together, mean apixaban AUC and Cmax were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or Cmax.

Effect on apixaban on other medicinal products
In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 >45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC50 >20 μM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes. Apixaban is not significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin: Co-administration of apixaban (20mg once a day) and digoxin (0.25mg once a day), a P-gp substrate did not affect digoxin AUC or Cmax. Apixaban does not inhibit P-gp mediated substrate transport.
Naproxen: Co-administration of single doses of apixaban (10mg) and naproxen (500mg), a commonly used NSAIDs, did not have any effect in the naproxen AUC or Cmax.
Atenolol: Co-administration of a single dose of apixaban (10mg) and atenolol (100mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.
Activated charcoal
Administration of activated charcoal reduces apixaban exposure.

PREGNANCY AND LACTATION
Pregnancy: There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is advisable to avoid the use apixaban during pregnancy.

Breast-feeding: It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from apixaban therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the women.

Fertility: Studies in animals dosed with apixaban have shown no effect on fertility.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES
Varexa has no or negligible influence on the ability to drive and use machines.

SIDE EFFECTS
Summary of the safety profile
The safety of apixaban has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1.7 years and 221 days respectively. Common adverse reactions were haemorrhage, confusion, epistaxis, and haematoma.

In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10% in the apixaban vs enoxaparin studies.

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study. In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

In the VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study.

Tabulated list of adverse reactions
Table 13 shows the adverse reactions ranked under headings of System Organ Class and
frequency using the following convention: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively.

Table 13: Tabulated adverse reactions

SYSTEM ORGAN CLASS	Prevention of VTEin adult patients who have undergone electivehip or knee replacement surgery (VTEp)	Prevention of strokeand systemic embolism in adult patients with NVAF, with one or more riskfactors (NVAF)	Treatment of DVT and PE and prevention of recurrent DVT andPE (VTEt)
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
Immune system disorders			
Hypersensitivity, allergic oedema, and Anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Angioedema	Not Known	Not Known	Not Known
Nervous system disorders			
Brain haemorrhage†	Not Known	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage,haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intra-abdominal haemorrhage	Not Known	Uncommon	Not Known
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not Known	Rare	Rare
Gastrointestinal disorders			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidalhaemorrhage	Not Known	Uncommon	Uncommon
Mouth haemorrhage	Not Known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not Known	Rare	Not Known
Hepatobiliary disorders			
Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphate increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gamma-glutamyl transferase increased	Uncommon	Common	Common
Alanine aminotransferase increased	Uncommon	Uncommon	Common
Skin and subcutaneous tissue disorders			
Skin rash	Not Known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Erythema multiforme	Not Known	Very Rare	Not Known
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Rare	Uncommon
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage,urogenital haemorrhage	Uncommon	Uncommon	Common
General disorders and administration site conditions			
Application sitebleeding	Not Known	Uncommon	Uncommon
Investigations			
Occult blood positive	Not Known	Uncommon	Uncommon
Injury, poisoning, and procedural complications			
Contusion	Common	Common	Common
Post procedural haemorrhage (including postprocedural haematoma, wound haemorrhage, vessel puncturesite haematoma and catheter site haemorrhage),wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Uncommon	Uncommon	Uncommon
Traumatic haemorrhage	Not Known	Uncommon	Uncommon

* There were no occurrence of generalized pruritus CV185057 (long-term prevention of VTE)
† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (i.e., haemorrhagic stroke or putamen, cerebellar, intraventricular, or, subdural haemorrhages)

The use of apixaban may be associated with an increased risk of occult or overt bleeding form any tissue or organ, which may result in post-haemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree of extent of the bleeding.

OVERDOSE
There is no antidote to apixaban available in Malaysia. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, i.e., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

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

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, and had no impact on Cmax. Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

For situation when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, administration of prothrombin complex concentration (PCCs) or recombinant factor VIIa may also be considered. Reversal of apixaban pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4 factor PCC products to reverse bleeding in individuals who have received apixaban. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

Haemodialysis decreased apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, Haemodialysis is unlikely to be an effective means of managing apixaban overdose.

PACK SIZE
Varexa Tablet 2.5 mg:
Blister packs of 10's per strip into 3 strips per box with packaging insert.
Blister packs of 10's per strip into 6 strips per box with packaging insert.

Varexa Tablet 5 mg:
Blister packs of 10's per strip into 3 strips per box with packaging insert.
Blister packs of 10's per strip into 6 strips per box with packaging insert.

STORAGE
Store below 30^{O}C.

SHELF LIFE
2 years

PRODUCT REGISTRATION HOLDER:
DUOPHARMA MANUFACTURING (BANGI) SDN BHD
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia

MANUFACTURER:
DUOPHARMA MANUFACTURING (BANGI) SDN BHD
Lot No. 2 & 4, , Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia

Revision Date: July 2024
150001XXXX XX

DUOPHARMA