SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

APIXABAN 2,5 mg VIATRIS (Film-coated tablets)

APIXABAN 5 mg VIATRIS (Film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

APIXABAN 2,5 mg VIATRIS:

Each film-coated tablet contains 2,5 mg apixaban.

Contains sugar: Lactose anhydrous 51,75 mg.

APIXABAN 5 mg VIATRIS:

Each film-coated tablet contains 5 mg apixaban.

Contains sugar: Lactose anhydrous 103,5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

APIXABAN 2,5 mg VIATRIS: Brown, film-coated, round, biconvex, beveled edge tablet debossed with X 2 on one side of the tablet and M on other side.

APIXABAN 5 mg VIATRIS: Brown, film-coated, oval, biconvex, beveled edge tablet, debossed with X 5 on one side of the tablet and M on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of VTE: elective hip or knee replacement surgery

APIXABAN VIATRIS is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Prevention of stroke and systemic embolism: nonvalvular atrial fibrillation (NVAF)

APIXABAN VIATRIS is also indicated to reduce the risk of stroke, systemic embolism and death in

patients with nonvalvular atrial fibrillation with one or more risk factors.

4.2 Posology and method of administration

APIXABAN VIATRIS can be taken with or without food.

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

Posology

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of APIXABAN VIATRIS 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 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: NVAF

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

Age, body weight, serum creatinine

In patients with at least 2 of the following characteristics, age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1,5 mg/dL (133 micromole/L), the recommended dose of APIXABAN VIATRIS is 2,5 mg twice daily.

Body weight

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see section 5.2).

Prevention of stroke and systemic embolism: NVAF

See section 4.2, Prevention of stroke and systemic embolism: NVAF, Age, body weight, serum clearance recommended dosage.

Converting from or to parenteral anticoagulants

In general, switching treatment from parenteral anticoagulants to APIXABAN VIATRIS (and vice versa) can be done at the next scheduled dose.

Converting from or to warfarin or other vitamin K antagonists (VKA)

When converting patients from warfarin or other VKA therapy to APIXABAN VIATRIS, discontinue warfarin or other VKA therapy and start APIXABAN VIATRIS when the INR is below 2,0.

When converting from APIXABAN VIATRIS to warfarin or other VKA therapy, continue APIXABAN VIATRIS for 48 hours after the first dose of warfarin or other VKA therapy.

Patients undergoing cardioversion

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

For patients not previously treated with anticoagulants, at least 5 doses of APIXABAN VIATRIS 5 mg twice daily (2,5 mg twice daily in patients who qualify for a dose reduction) should be given before cardioversion to ensure adequate anticoagulation.

If cardioversion is required before 5 doses of APIXABAN VIATRIS 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 patient meets the criteria for dose reduction. The administration of the loading dose should be given at least 2 hours before cardioversion.

Confirmation should be sought prior to cardioversion that the patient has taken APIXABAN VIATRIS as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Special populations

Renal impairment

Prevention of VTE: elective hip or knee replacement surgery

In surgical patients, no dose adjustment is necessary in patients with mild, moderate or severe (creatine clearance 15 – 29 mL/min) renal impairment (see section 5.2). Because there is limited clinical experience in patients with creatinine clearance < 15 mL/min and there are no data in patients undergoing dialysis, APIXABAN VIATRIS is not recommended in these patients (see section 4.4 and section 5.2).

Prevention of stroke and systemic embolism: NVAF

In patients with AF, no dose adjustment is recommended in patients with creatinine clearance 15 to 29 mL/min, except as described under section 4.2, Prevention of stroke and systemic embolism: NVAF. Because there is no clinical experience in patients with creatinine clearance < 15 mL/min, a dosing

recommendation cannot be provided.

There are no data in patients undergoing dialysis, therefore, APIXABAN VIATRIS is not recommended in these patients.

Hepatic impairment

APIXABAN VIATRIS may 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 (see section 4.4 and section 5.2).

APIXABAN VIATRIS is not recommended in patients with severe hepatic impairment (see section 4.4 and section 5.2).

Elderly population

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see section 5.2).

Prevention of stroke and systemic embolism: NVAF

See section 4.2, Posology and method of administration, Prevention of stroke and systemic embolism: NVAF.

Surgery and invasive procedures

APIXABAN VIATRIS should be discontinued 2 to 3 days prior to elective surgery or invasive procedures such as neuraxial regional anaesthesia. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Paediatric and adolescent

The efficacy and safety of APIXABAN VIATRIS is children below age 18 have not been established. No data are available.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to apixaban or to any of the excipients (listed in section 6.1).
- Clinically significant active bleeding.

- APIXABAN VIATRIS is not recommended in patients with severe renal disease (CrCl < 15 mL/min).
- APIXABAN VIATRIS is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- APIXABAN VIATRIS should not be administered with antiplatelet medicines other than aspirin (see section 4.4).
- Patients with antiphospholipid syndrome (APS) with persistent positivity for all three antiphospholipid antibodies (patients with triple positive APS).

4.4 Special warnings and precautions for use

Haemorrhage risk

Patients taking APIXABAN VIATRIS are to be carefully observed for signs of bleeding. APIXABAN VIATRIS is recommended to be used with caution in conditions with increased risk of haemorrhage, such as congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, bacterial endocarditis, thrombocytopenia, platelet disorders, history of haemorrhagic stroke, severe uncontrolled hypertension, and recent brain, spinal or ophthalmological surgery. APIXABAN VIATRIS administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the event of haemorrhagic complications, treatment must be discontinued, and the source of bleeding investigated. The initiation of appropriate treatment e.g. surgical haemostasis or the transfusion of fresh frozen plasma, should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is no clinical experience with the use of 4-factor PCC medicines to reverse bleeding in individuals who have received apixaban. Reversal of apixaban pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, has been demonstrated after administration of 4-factor PCCs in healthy subjects. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Standard anticoagulation tests cannot be used to monitor APIXABAN VIATRIS (see section 4.5).

There is no reversal medication for APIXABAN VIATRIS.

Temporary discontinuation of APIXABAN VIATRIS

Discontinue APIXABAN VIATRIS in the presence of active bleeding, elective surgery, or invasive

procedures that place patients at an increased risk of haemorrhage. Restart APIXABAN VIATRIS therapy 12 – 24 hours after the danger of haemorrhage has ceased.

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

APIXABAN VIATRIS can be administered with caution in patients receiving concomitant systemic treatment with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g. ritonavir). These medicines may increase APIXABAN VIATRIS exposure by 2-fold (see section 4.5).

Interaction with strong inducers of both CYP3A4 and P-gp

The concomitant use of APIXABAN VIATRIS with strong CYP3A4 and P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may lead to a ~50 % reduction in apixaban exposure. Use caution when co-administering APIXABAN VIATRIS with strong inducers of both CYP3A4 and P-gp (see section 4.5).

For the treatment of DVT of PE, APIXABAN VIATRIS is not recommended in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp (see section 4.5). For prevention of recurrent DVT and PE, use caution when co-administering APIXABAN VIATRIS with strong inducers of both CYP3A4 and P-gp (see section 4.5).

Interaction with other medicines affecting haemostasis

The concomitant use of APIXABAN VIATRIS with antiplatelet medicines increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.

Other platelet aggregation inhibitors or other antithrombotic medicines are not recommended concomitantly with APIXABAN VIATRIS following surgery (see section 4.5).

In patients with atrial fibrillation and a condition that warrants chronic use of aspirin, APIXABAN VIATRIS may be used with due regard to increased risk of major bleeding. In a clinical trial of patients with atrial fibrillation, concomitant use of aspirin 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.

Patients with prosthetic heart valves

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

Patients with antiphospholipid syndrome

Treatment of patients with established APS is not recommended as evidence regarding safety and efficacy, including the benefit/harm balance of APIXABAN VIATRIS in patients with APS, is inconclusive/incomplete. There is some evidence that treatment with APIXABAN VIATRIS may be associated with an increased risk of recurrent arterial thrombotic events in patients with APS compared to treatment of these patients with warfarin, a vitamin K antagonist.

Surgery and invasive procedures

APIXABAN VIATRIS should be discontinued 2 to 3 days prior to elective surgery or invasive procedures such as neuraxial regional anaesthesia. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Temporary discontinuation of APIXABAN VIATRIS

Discontinue APIXABAN VIATRIS in the presence of active bleeding, elective surgery, or invasive procedures that place patients at an increased risk of haemorrhage. Restart APIXABAN VIATRIS therapy 12 – 24 hours after the danger of haemorrhage has ceased.

Spinal/epidural anaesthesia or puncture

Prevention of VTE: elective hip or knee replacement surgery

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines, such as APIXABAN VIATRIS, 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 medicines affecting haemostasis. When an indwelling epidural or intrathecal catheter is planned, APIXABAN VIATRIS should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of APIXABAN VIATRIS. 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 medical practitioner should consider the potential benefit versus the risk of anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Hip fracture surgery

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

Laboratory parameters

Clotting tests e.g. prothrombin time (PT), INR and activated partial thromboplastin time (aPTT) are affected as expected by the mechanism of action of APIXABAN VIATRIS (see section 5.1). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see section 5.1). These parameters should not be used to monitor APIXABAN VIATRIS therapy.

Special populations

Renal impairment

Prevention of VTE: elective hip or knee replacement surgery

Because there is limited clinical experience in patients with creatinine clearance < 15 mL/min and there are no data in patients undergoing dialysis, APIXABAN VIATRIS is not recommended in these patients (see section 4.2, section 5.2 and section 4.3).

Prevention of stroke and systemic embolism: NVAF

APIXABAN VIATRIS has not been studied in patients undergoing dialysis and is not recommended in these patients.

Hepatic impairment

APIXABAN VIATRIS is not recommended in patients with severe hepatic impairment (see section 5.1 and section 4.3).

APIXABAN VIATRIS may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see section 4.2 and section 5.1).

Paediatric use

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

Lactose intolerance

APIXABAN VIATRIS contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take APIXABAN VIATRIS.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on APIXABAN VIATRIS

Inhibitors of CYP3A4 and P-gp

Co-administration of APIXABAN VIATRIS 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 VIATRIS AUC and a 1,6-fold increase in mean apixaban C_{max} (see section 4.4).

The dose of APIXABAN VIATRIS must not exceed 2,5 mg twice daily when used with these medicines. Active substances that are not considered strong inhibitors of both CYP3A4 and P-gp (e.g. diltiazem, naproxen, amiodarone, clarithromycin, verapamil, quinidine) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for APIXABAN VIATRIS is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1,4-fold increase in mean APIXABAN VIATRIS AUD and 1,3-fold increase in C_{max}. 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 VIATRIS and C_{max}, 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 VIATRIS AUC and C_{max} 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 C_{max}, respectively. The concomitant use of APIXABAN VIATRIS with other strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John’s Wort) may also lead to reduced APIXABAN VIATRIS

plasma concentrations. No dose adjustment for APIXABAN VIATRIS is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.4).

For the treatment of DVT and PE, concomitant therapy with strong inducers of both CYP3A4 and P-gp is not recommended (see section 4.4). For prevention of recurrent DVT and PE, strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.4).

Anticoagulants, platelet aggregation inhibitors and NSAIDs

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

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

Apixaban co-administered with clopidogrel (75 mg once daily) or with the combination of clopidogrel 75 mg and aspirin 162 mg once daily in Phase 1 studies did not show a relevant increase in bleeding time or further inhibition of platelet aggregation compared to administration of the antiplatelet agents without APIXABAN VIATRIS. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban with clopidogrel, ticagrelor or other antiplatelet medicines, except aspirin, are not recommended due to the resulting associated increased risk of major bleeds (see section 4.3).

Naproxen (500 mg), and inhibitor of P-gp, led to a 1,5-fold and 1,6-fold increase in mean apixaban AUC and C_{max}, in healthy subjects, respectively. Corresponding increases in clotting tests were observed for apixaban. No clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

APIXABAN VIATRIS should be used with caution when co-administered with NSAIDs (including aspirin) because these medicinal products typically increase the bleeding risk.

Medicines associated with serious bleeding are not recommended concomitantly with APIXABAN VIATRIS, such as unfractionated heparins and heparin derivatives (including low molecular weight heparins (LMWH)), FXa inhibiting oligosaccharides (e.g. fondaparinux), direct thrombin II inhibitors (e.g. desirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, dipyridamole, dextran, sulfinpyrazone, vitamin K antagonists, and other oral anticoagulants. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section

4.4).

Other concomitant therapies

No clinically 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 medicines together, mean apixaban AUC and C_{max} were 15 % and 18 % lower than administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.

Effect of APIXABAN VIATRIS on other medicines

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 mM) and weak inhibitory effect on the activity of CYP2C19 (IC50 > 20 mM) 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 mM. Therefore, APIXABAN VIATRIS is not expected to alter the metabolic clearance of co-administered medicines that are metabolized by these enzymes. APIXABAN VIATRIS 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 (20 mg once a day) and digoxin (0,25 mg once a day), a P-gp substrate, did not affect digoxin AUC or C_{max}. Therefore, APIXABAN VIATRIS does not inhibit P-gp mediated substrate transport.

Naproxen

Co-administration of single doses of apixaban (10 mg) and naproxen (500 mg) did not have any effect on the naproxen AUC or C_{max}.

Atenolol

Co-administration of a single dose of apixaban (10 mg) and atenolol (100 mg) did not alter the pharmacokinetics of atenolol.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety has not been established.

Pregnancy

APIXABAN VIATRIS is not recommended during pregnancy. Treatment may increase the risk of haemorrhage during pregnancy and delivery.

Breastfeeding

It is unknown whether APIXABAN VIATRIS or its metabolites are excreted in human milk. A risk to newborns and infants cannot be excluded.

Women taking APIXABAN VIATRIS should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Prevention of VTE: elective hip or knee replacement surgery

The safety of apixaban has been evaluated in 5 924 patients exposed to apixaban 2,5 mg twice daily undergoing major orthopaedic 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 may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anaemia, haemorrhage, contusion and nausea. The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ (see section 4.4).

Tabulated list of adverse reactions

Table 1 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: Frequent; Less frequent; Frequency unknown.

Table 1: Tabulated adverse reactions

System organ class	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
Blood and lymphatic system disorders			
Anaemia	Frequent	Frequent	Frequent
Thrombocytopenia	Less frequent	Less frequent	Frequent
Immune system disorders			
Hypersensitivity, allergic oedema and anaphylaxis	Less frequent	Less frequent	Less frequent
Pruritus	Less frequent	Less frequent	Less frequent *
Angioedema	Frequency unknown	Frequency unknown	Frequency unknown
Nervous system disorders			
Brain haemorrhage[†]	Frequency unknown	Less frequent	Less frequent
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Less frequent	Frequent	Less frequent
Vascular disorders			
Haemorrhage, haematoma	Frequent	Frequent	Frequent
Hypotension (including procedural hypotension)	Less frequent	Frequent	Less frequent
Intra-abdominal haemorrhage	Frequency unknown	Less frequent	Frequency unknown

Respiratory, thoracic and mediastinal disorders			
Epistaxis	Less frequent	Frequent	Frequent
Haemoptysis	Less frequent	Less frequent	Less frequent
Respiratory tract haemorrhage	Frequency unknown	Less frequent	Less frequent
Gastrointestinal disorders			
Nausea	Frequent	Frequent	Frequent
Gastrointestinal haemorrhage	Less frequent	Frequent	Frequent
Haemorrhoidal haemorrhage	Frequency unknown	Less frequent	Frequent
Mouth haemorrhage	Frequency unknown	Less frequent	Frequent
Haematochezia	Less frequent	Less frequent	Less frequent
Rectal haemorrhage, gingival bleeding	Less frequent	Frequent	Frequent
Retroperitoneal haemorrhage	Frequency unknown	Less frequent	Frequency unknown
Hepatobiliary disorders			
Liver function test abnormal, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased blood bilirubin	Less frequent	Less frequent	Less frequent
Increased gamma-glutamyltransferase	Less frequent	Frequent	Frequent
Increased alanine aminotransferase	Less frequent	Less frequent	Frequent

Skin and subcutaneous tissue disorders			
Skin rash	Frequency unknown	Less frequent	Frequent
Alopecia	Less frequent	Less frequent	Less frequent
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Less frequent	Less frequent	Less frequent
Renal and urinary disorders			
Haematuria	Less frequent	Frequent	Frequent
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Less frequent	Less frequent	Frequent
General disorders and administration site conditions			
Application site bleeding	Frequency unknown	Less frequent	Less frequent
Investigations			
Positive occult blood	Frequency unknown	Less frequent	Less frequent
Injury, poisoning and procedural complications			
Contusion	Frequent	Frequent	Frequent

Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Less frequent	Less frequent	Less frequent
Traumatic haemorrhage	Frequency unknown	Less frequent	Less frequent

*There were no occurrences of generalized pruritus in 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no antidote to apixaban. Overdose of apixaban may result in a higher risk of bleeding.

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 C_{max}. 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 VIATRIS overdose or accidental ingestion.

Haemodialysis is unlikely to be an effective means of managing APIXABAN VIATRIS overdose.

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants

Mechanism of action

Apixaban is an inhibitor of coagulation factor Xa (FXa). Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development.

The pharmacodynamic effects of apixaban are reflective of the mechanism of action. As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT). However, changes observed in these clotting tests are not suitable for assessing the effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in the Rotachrom® Heparin chromogenic assay. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom® assay is within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in situations where knowledge of apixaban exposure may help to inform clinical decisions.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of apixaban is approximately 50 % for doses up to 10 mg. Apixaban is absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg, apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~20 % CV and ~30 % CV, respectively.

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of applesauce the C_{max} and AUC were 21 % and 16 % lower, respectively, when compared to administration of 2 whole 5 mg tablets.

Following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of D5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose.

Distribution

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

Biotransformation and elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25 % was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27 % of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3,3 L/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major medicine-related component in

human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-gp and breast cancer resistance protein (BCRP).

Special populations

Renal impairment

There was no impact of impaired renal function on peak concentration of apixaban after a single dose. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51 – 80 mL/min), moderate (creatinine clearance 30 – 50 mL/min) and severe (creatinine clearance 15 – 29 mL/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44 % respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity (see section 4.2, Prevention of stroke and systemic embolism: NVAF).

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36 % when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14 % in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min.

Hepatic impairment

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease. Apixaban is not recommended in patients with severe hepatic impairment (see section 4.4).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child Pugh A and B, respectively) to healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with mild or moderate hepatic impairment. Changes in anti-FXa activity and INR were comparable between subjects with mild to moderate hepatic impairment. However, given the limited number of subjects studied, caution is advised when using APIXABAN VIATRIS in this population (see section 4.2 and section 4.4).

Elderly population

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32 % higher (see section 4.2).

Body weight

Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30 % lower exposure and body weight < 50 kg was associated with approximately 30 % higher exposure (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0,5 – 50 mg). The relationship between apixaban plasma concentration and anti-FXa activity was best described by a linear model. The PK/PD relationship observed in patients who received apixaban in Phase 2 or Phase 3 clinical trials was consistent with that established in healthy subjects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Uncoated tablet

Cellulose microcrystalline (Avicel PH-113)

Croscarmellose sodium (Ac-di-sol)

Lactose anhydrous (impalpable)

Magnesium stearate

Sodium lauryl sulphate (Kolliphore SLS fine)

Film-coating

Insta-coat Universal Brown (A05R04319)

Hypromellose

Polyethylene glycol

Red iron oxide

Sodium lauryl sulfate

Titanium dioxide

Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Do not remove the blisters from the outer carton until required for use.

Store in the original container.

6.5 Nature and contents of container

APIXABAN 2,5 mg VIATRIS: PVC/PVDC blister pack comprising of clear, transparent PVC and hard tampered aluminium foil coated with heat seal lacquer. Packed in a carton. One 1 blister of 10 film-coated tablets each. Pack sizes: 10’s.

APIXABAN 5 mg VIATRIS: PVC/PVDC blister pack comprising of clear, transparent PVC and hard tampered aluminium foil coated with heat seal lacquer. Packed in a carton. One blister of 10 film-coated tablets each. Pack sizes: 10’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

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Isando

Kempton Park

Gauteng, 1601

Tel. no.: +2711 451 1300

8 REGISTRATION NUMBERS

APIXABAN 2,5 mg VIATRIS: 57/8.2/0355.353

APIXABAN 5 mg VIATRIS: 57/8.2/0356.354

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

22 July 2025

10 DATE OF REVISION OF THE TEXT

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