Initial submission: 19/11/2020 (0000)
Clinical screening query as per SAHPRA email dated 10/06/2022: submitted 27/06/2022 (0002)
PEM unit response dated 23/08/2023 (0003)
Submission of Final PI as per email received 12/10//2023: submitted 23/10/2023

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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APIXABAN 2,5 ACCORD (Film-coated tablet)

APIXABAN 5 ACCORD (Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Contains sugar:

APIXABAN 2,5 ACCORD: Each film-coated tablet contains 51,97 mg lactose (see section 4.4).

APIXABAN 5 ACCORD: Each film-coated tablet contains 103,95 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

APIXABAN 2,5 ACCORD: Yellow, round shaped, approximately 6,00 mm in diameter, biconvex, film coated tablet debossed with "IU1" on one side and plain on other side.

APIXABAN 5 ACCORD: Pink, oval shaped, approximately 9,8 mm in length, 5,2 mm in width, biconvex, film coated tablet debossed with "IU2" on one side and plain on other side.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

Prevention of VTE: elective hip or knee replacement surgery

APIXABAN ACCORD 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 ACCORD** 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

Posology

Recommended dosage

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of **APIXABAN ACCORD** 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 ACCORD** 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 micromol/l), the recommended dose of **APIXABAN ACCORD** is 2,5 mg twice daily.

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 (creatinine 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 ACCORD** is not recommended in these patients (see section 4.4, Renal impairment, Prevention of VTE: elective hip or knee replacement surgery 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 ACCORD** is not recommended in these patients.

Hepatic impairment

APIXABAN ACCORD 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, Hepatic impairment and section 5.2).

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

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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 above under Recommended dosage, Prevention of stroke and systemic embolism: NVAF.

Elderly

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 above under Recommended dosage, Prevention of stroke and systemic embolism: NVAF.

Converting from or to parenteral anticoagulants

In general, switching treatment from parenteral anticoagulants to **APIXABAN ACCORD** (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 ACCORD**, discontinue warfarin or other VKA therapy and start **APIXABAN ACCORD** when the INR is below 2,0.

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

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Surgery and invasive procedures

APIXABAN ACCORD 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 population

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

Method of administration

APIXABAN ACCORD can be taken with or without food.

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

4.3 Contraindications

- Hypersensitivity to the active substance (apixaban) or to any of the excipients of **APIXABAN ACCORD** listed in section 6.1.
- Clinically significant active bleeding.
- **APIXABAN ACCORD** is not recommended in patients with severe renal disease (CrCl < 15 ml/min).
- **APIXABAN ACCORD** is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

- **APIXABAN ACCORD** should not be administered with anti-platelet medicines other than aspirin (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk

Patients taking **APIXABAN ACCORD** are to be carefully observed for signs of bleeding. It 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 ACCORD** administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9).

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 (see section 5.1).
There are no reversal medication for **APIXABAN ACCORD**.

Temporary discontinuation of **APIXABAN ACCORD**

Discontinue **APIXABAN ACCORD**, in the presence of active bleeding, elective surgery, or invasive procedures that place patients at an increased risk of haemorrhage. Lapses in therapy should be avoided and restart **APIXABAN ACCORD** therapy 12-24 hours after the danger of haemorrhage has ceased.

Interaction with other medicinal products affecting haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of **APIXABAN ACCORD** with antiplatelet medicines increases the risk of bleeding (see section 4.5).

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 drugs (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with **APIXABAN ACCORD** (see section 4.5).

In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with **APIXABAN ACCORD**.
In 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 trial, there was limited (2.1 %) use of concomitant dual antiplatelet therapy (see section 5.1).

A patient with atrial fibrillation with (acute coronary syndrome) ACS and/or undergoing (percutaneous coronary intervention) 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 (see section 5.1).

In 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 medicines for the treatment of acute ischemic stroke

There is very limited experience with the use of thrombolytic medicines for the treatment of acute ischemic stroke in patients administered apixaban. (see section 4.5).

Patients with prosthetic heart valves

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

Patients with antiphospholipid syndrome

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

Surgery and invasive procedures

APIXABAN ACCORD should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

APIXABAN ACCORD should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedures 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 ACCORD 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 cardioversion see section 4.2).
For patients undergoing catheter ablation for atrial fibrillation, **APIXABAN ACCORD** treatment does not need to be interrupted (see sections 4.2, 4.3 and 4.5).

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines 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~~ 6 hours prior to the first dose of **APIXABAN ACCORD**. 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 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 (pharmacokinetic) 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 ACCORD is not recommended as an alternative to unfractionated heparin in

patients with 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

Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established.

Patients with renal impairment

Limited clinical data indicate that 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 of 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)
(see sections 4.2 and 5.2).

For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2).
In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore, **APIXABAN ACCORD** is not recommended (see sections 4.2 and 5.2).

Elderly patients

Increasing age may increase haemorrhagic risk (see section 5.2).

Also, the coadministration of **APIXABAN ACCORD** with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Body weight

Low body weight (< 60 kg) may increase haemorrhagic risk (see section 5.2).

Patients with hepatic impairment

APIXABAN ACCORD is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see section 5.2).
It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2and 5.2).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore, **APIXABAN ACCORD** should be used cautiously in this population (see section 5.2). Prior to initiating **APIXABAN ACCORD**, liver function testing should be performed.

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

The use of **APIXABAN ACCORD** is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole,

voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir). These medicinal products may increase apixaban exposure by 2-fold (see section 4.5), or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp

The concomitant use of **APIXABAN ACCORD** 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. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration 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 (see section 4.5):

- 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 trials 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 tests [e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by the 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 (see section 5.1).

Information about excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and P-gp

Coadministration 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 ACCORD** is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg., 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 coadministered with medicines 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

Coadministration 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 (e.g., phenytoin, carbamazepine, phenobarbitone 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 of both CYP3A4 and P-gp since efficacy may be compromised (see section 4.4).

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 (see section 4.3).

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg 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 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily, or with prasugrel (60 mg followed by 10 mg once daily) in Phase I studies did not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the antiplatelet agents without apixaban. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects 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 changes were 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 ACCORD** 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 (see section 4.4).

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 ACCORD** is not recommended (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. Coadministration 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 of 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 coadministered medicinal products that are metabolised by these enzymes. Apixaban is not a 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

Coadministration 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 Cmax. Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen

Coadministration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or Cmax.

Atenolol

Coadministration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

Activated charcoal

Administration of activated charcoal reduces apixaban exposure (see section 4.9).

4.6 Fertility, 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. Apixaban is not recommended 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. In rat milk, a high milk to maternal plasma ratio (Cmax about 8, AUC about 30) was found, possibly due to active transport into the milk. A risk to newborns and infants cannot be excluded.

APIXABAN ACCORD treatment is not recommended for mothers who are breastfeeding their infants.

Fertility

Studies in animals dosed with apixaban have shown no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

Common adverse reactions were anaemia, haemorrhage, contusion, epistaxis, and haematoma (see Table 1 for adverse reaction profile and frequencies by indication).

b. Tabulated list of adverse reactions

Table 1 below shows the adverse reactions ranked under headings of system organ class and frequency

Table 1: ADRs

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)**

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Blood and lymphatic system disorders			
Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)	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 (inculding haematemesis and melaena)	Less frequent	Frequent	Frequent
Haemorrhoidal haemorrhage	Frequency unknown	Less frequent	Less 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, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Less frequent	Less frequent	Less frequent
Gamma-glutamyltransferase increased	Less frequent	Frequent	Frequent
Alanine aminotransferase increased	Less frequent	Less frequent	Frequent
Skin and subcutaneous tissue disorders			
Skin rash	Frequency unknown	Less frequent	Frequent
Alopecia	Less frequent	Less frequent	Less frequent
Erythema multiforme	Frequency unknown	Frequency unknown	Frequency unknown
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			
Occult blood positive	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 generalised pruritus in CV185057 (long term prevention of VTE)

† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (ie., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages, subarachnoid haemorrhage and spinal haematoma).

The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding (see sections 4.4 and 5.1).

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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, e.g., surgical haemostasis, the transfusion of fresh frozen plasma should be considered.

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 effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban reduced mean apixaban AUC by 50 % and 27 %, respectively, 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 situations when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, a reversal agent for factor Xa inhibitors is available (see section 4.4). Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered. Reversal of **APIXABAN ACCORD** 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 ACCORD**. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Initial submission: 19/11/2020 (0000)
Clinical screening query as per SAHPRA email dated 10/06/2022: submitted 27/06/2022 (0002)
PEM unit response dated 23/08/2023 (0003)
Submission of Final PI as per email received 12/10//2023: submitted 23/10/2023

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Pharmacological classification: A 8.2 Anticoagulants

Mechanism of action

Apixaban is an inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

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 normalised ratio (INR) and activated partial thromboplastin time (aPTT). However, changes observed in these clotting tests are not suitable for assessing the effects of apixaban.

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

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Absorption

The absolute bioavailability of apixaban is approximately 50 % for doses up to 10 mg. Apixaban is absorbed with maximum concentrations (Cmax) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or Cmax 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 apple puree, the Cmax and AUC were 21 % and 16 % lower, respectively, when compared to administration of 2 whole 5 mg tablets. The reduction in exposure is not considered clinically relevant.

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.
Given the predictable, dose-proportional pharmacokinetic profile of apixaban, the bioavailability results from the conducted studies are applicable to lower apixaban doses.

Distribution

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

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 metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-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).

Renal impairment

There was no impact of impaired renal function on peak concentration of apixaban. 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.

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. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment

In a study comparing 8 subjects with mild hepatic impairment, Child-Pugh A score 5 (n = 6) and score 6 (n = 2), and 8 subjects with moderate hepatic impairment, Child-Pugh B score 7 (n = 6) and score 8 (n = 2), to 16 healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32 % higher and no difference in Cmax.

Gender

Exposure to apixaban was approximately 18 % higher in females than in males.

Ethnic origin and race

The results across phase I studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population pharmacokinetic analysis in patients who received apixaban were generally consistent with the phase I results.

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.

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-Factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose

Cellulose, microcrystalline (PH 102)

Croscarmellose sodium

Sodium laurilsulfate

Magnesium stearate

Film-coating

Hypromellose

Lactose monohydrate

Titanium dioxide

Triacetin

Iron oxide yellow (E172) (2,5 mg)

Iron oxide red (E172) (5 mg)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

PVC/PVDC-Alu blister and HDPE bottle packs.

Pack size: PVC/PVdC-Aluminium blisters are available in 10, 14, 20, 28, 56, 60, 100, 112, 168, and 200 film-coated tablets.

HDPE bottle containing 60, 100, 168, 180, 200 and 1000 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of

in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place,

Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

APIXABAN 2,5 ACCORD : 55/8.2/0372

APIXABAN 5 ACCORD : 55/8.2/0373

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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03 October 2023

10. DATE OF REVISION OF THE TEXT

03 October 2023