

APPROVED PROFESSIONAL INFORMATION
Dr. Reddy's Laboratories (Pty) Ltd.
APIXABAN 2,5/ 5 DRL (film-coated tablets)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APIXABAN 2,5 DRL film-coated tablet

APIXABAN 5 DRL film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

76,84 mg lactose (as anhydrous) per tablet

APIXABAN 5 DRL: Each film-coated tablet contains apixaban 5 mg.

Excipient with known effect:

153;68 mg lactose (as anhydrous) per tablet.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

APIXABAN 2,5 DRL: White to off white colored, round shaped, biconvex, film coated tablet, debossed with '2.5' on one side and a "Y" (logo) on the other side.

APIXABAN 5 DRL: White to off white colored, oval shaped, biconvex, film coated tablet, debossed with '5' on one side and "Y" (logo) on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolic events (VTE): elective hip or knee replacement surgery

APIXABAN DRL is indicated for the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.

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

APIXABAN DRL is also indicated to reduce the risk of stroke, systemic embolism, and death in patients with NVAF with one or more risk factors.

4.2 Posology and method of administration

Posology

Prevention of VTE: elective hip or knee replacement surgery

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

Age, body weight, serum creatinine: In patients with at least 2 of the following characteristics, age \geq 80 years, body weight \leq 60 kg, or serum creatinine \geq 1,5 mg/dL (133 micromol/L), the recommended dose of APIXABAN DRL is 2,5 mg twice daily.

Special population

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 to 29 ml/min) renal impairment (see Sections 5.1 and 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 DRL is not recommended in these patients (see Sections 4.4, 5.1 and 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 DRL is not recommended in these patients.

Hepatic impairment

APIXABAN DRL 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 Sections 4.4, 5.1 and 5.2).

APIXABAN DRL is not recommended in patients with severe hepatic impairment (see Sections 4.4, 5.1 and 5.2).

Bodyweight

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see Sections 5.1 and 5.2).

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Prevention of stroke and systemic embolism: NVAF

See Section 4.2, Prevention of stroke and systemic embolism: NVAF.

Elderly

Prevention of VTE: elective hip or knee replacement surgery

No dose adjustment required (see Sections 5.1 and 5.2).

Prevention of stroke and systemic embolism: NVAF

See Section 4.2, Prevention of stroke and systemic embolism: NVAF.

Converting from or to parenteral anticoagulants

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

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

Surgery and invasive procedures

APIXABAN DRL 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 DRL in children below age 18 have not been established.

No data are available.

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Method of administration

APIXABAN DRL can be taken with or without food.

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

4.3 Contraindications

- Hypersensitivity to apixaban or any of the excipients of APIXABAN DRL film-coated tablets listed in Section 6.1.
- Clinically significant active bleeding.
- APIXABAN DRL is not recommended in patients with severe renal disease (CrCl <15 ml/min).
- APIXABAN DRL is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- APIXABAN DRL should not be administered with antiplatelet medicines other than aspirin (see Section 4.4).

4.4 Special warnings and precautions for use

Haemorrhage risk:

Patients taking APIXABAN DRL are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage, 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 DRL administration should be discontinued if severe haemorrhage occurs (see Sections 4.8 and 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

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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 currently no experience with the use of recombinant factor VIIa in individuals receiving APIXABAN DRL. Standard anticoagulation tests cannot be used to monitor APIXABAN DRL (see Section 4.5).

There is no reversal medication for APIXABAN DRL

Interaction with other medicines 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 DRL 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 (ASA).

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with APIXABAN DRL (see Section 4.5).

In patients with atrial fibrillation and a condition that warrants chronic use of aspirin, APIXABAN DRL 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 DRL have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of APIXABAN DRL is not recommended in this setting.

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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 DRL 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 DRL 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 DRL 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 DRL treatment does not need to be interrupted (see Sections 4.3 and 4.5).

Temporary discontinuation:

Discontinuing anticoagulants, including APIXABAN DRL, 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 DRL must be temporarily discontinued for any

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reason, therapy should be restarted as soon as possible (12 to 24 hours after the danger of the haemorrhage has ceased).

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 medicines affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of APIXABAN DRL. 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 PK characteristics of apixaban, a time interval of 20 to 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 medicines, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

Patients with renal impairment:

Limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15 to 29 mL/min) which may lead to an increased bleeding risk.

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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 to 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 to 29 mL/min), and patients with serum creatinine $\geq 1,5$ 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 is not recommended (see Sections 4.2 and 5.2).

Patients with hepatic impairment:

APIXABAN DRL 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 4.2 and 5.2).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin $\geq 1,5$ x ULN were excluded in clinical trials.

Therefore, APIXABAN DRL should be used cautiously in this population (see Section 5.2). Prior to initiating APIXABAN DRL, liver function testing should be performed.

Elderly patients:

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

Also, the coadministration of APIXABAN DRL 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).

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

The use of APIXABAN DRL 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 medicines 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 DRL with strong CYP3A4 and P-gp inducers (e.g., 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 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 DRL 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

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clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see Section 5.1).

Lactose:

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

Paediatric use:

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

4.5 Interaction with other medicines and other forms of interaction

Inhibitors of CYP3A4 and P-gp

Co-administration of APIXABAN DRL 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 C_{max} .

The dose of APIXABAN DRL must not exceed 2,5 mg twice daily when used with these medicines. Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (e.g., amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for APIXABAN DRL 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 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 AUC 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 AUC and C_{max} respectively.

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Inducers of CYP3A4 and P-gp

Co-administration of APIXABAN DRL 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 DRL with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced APIXABAN DRL plasma concentrations. No dose adjustment for APIXABAN DRL is required during concomitant therapy with such medicines, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp APIXABAN DRL 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.

Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs 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. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban alone. However the co-administration 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), an 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.

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APIXABAN DRL 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 DRL, 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, Interaction with other medicinal products affecting haemostasis).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when APIXABAN DRL 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 when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max} .

Clotting tests (e.g., PT, INR, and aPTT) are affected as expected by the mechanism of action of APIXABAN DRL (see section 5.1, PHARMACOLOGICAL ACTION, Pharmacodynamic properties). 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, PHARMACOLOGICAL ACTION, Pharmacodynamic properties). These parameters should not be used to monitor APIXABAN DRL therapy.

Effect of APIXABAN DRL on other medicines

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 ($IC_{50} > 45 \mu M$) and weak inhibitory effect on the activity

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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 medicines that are metabolised by these enzymes. APIXABAN DRL 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

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 DRL does not inhibit P-gp mediated substrate transport.

Naproxen

Co-administration 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 C_{max}.

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 DRL exposure (see Section 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of APIXABAN DRL in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. APIXABAN DRL is not recommended during pregnancy.

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Lactation

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

APIXABAN DRL therapy is not recommended for mothers who are breastfeeding their infants.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse drug reactions are classified according to the organ or system affected and listed in the tables below:

Table 1: Treatment-emergent adverse reactions in post-surgery orthopaedic patients

	Frequent	Less frequent
Blood and lymphatic system disorders	Anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)	Thrombocytopenia
Immune system disorders		Hypersensitivity, allergic oedema, anaphylaxis, pruritis
Eye disorders		Ocular haemorrhage (including conjunctival haemorrhage)
Vascular disorders	Haemorrhage (including haematoma, and vaginal and urethral haemorrhage)	Hypotension (including procedural hypotension)
Respiratory, thoracic and mediastinal disorders		Epistaxis, haemoptysis, Respiratory tract haemorrhage
Gastrointestinal disorders	Nausea	Gastrointestinal haemorrhage

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		(including haematemesis and melaena), haematochesia, rectal haemorrhage, gingival bleeding
Hepatobiliary disorders		Increased transaminases (including increased alanine aminotransferase and increased aspartate aminotransferase, increased. gamma-glutamyltransferase, abnormal liver function test, increased blood alkaline phosphatase, increased blood bilirubin
Skin and subcutaneous tissue disorders		Skin rash, alopecia
Musculoskeletal and connective tissue disorders		Muscle haemorrhage
Renal and urinary disorders		Haematuria (including respective laboratory parameters)
Injury, poisoning and procedural complications	Contusion	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

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Table 2: Treatment-emergent adverse reactions in NVAf patients

	Frequent	Less frequent
Blood and lymphatic system disorders	Anaemia	Thrombocytopenia
Immune system disorders		Hypersensitivity (including medicine hypersensitivity such as skin rash and anaphylactic reaction such as allergic oedema)
Nervous system disorders		Brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)
Eye disorders	Eye haemorrhage (including conjunctival haemorrhage)	
Vascular disorders	Other haemorrhage haematoma, hypotension (including procedural hypotension)	Intra-abdominal haemorrhage
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis, respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal haemorrhage)
Gastrointestinal disorders	Gastrointestinal haemorrhage (including haematemesis and melaena), rectal haemorrhage, gingival bleeding, nausea	Haemorrhoidal haemorrhage, haematochesia, mouth haemorrhage, retroperitoneal haemorrhage
Hepato-biliary disorders	Gamma-glutamyltransferase increased	Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, alanine aminotransferase increased
Skin and subcutaneous tissue disorders		Skin rash, alopecia
Musculoskeletal and connective tissue disorders		Muscle haemorrhage
Renal and urinary disorders	Haematuria	

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Reproductive system and breast disorders		Abnormal vaginal haemorrhage, urogenital haemorrhage
Investigations		Application site bleeding, Occult blood positive
Injury, poisoning and procedural complications	Contusion	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, traumatic haemorrhage

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 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

There is no antidote to APIXABAN DRL. Overdose of APIXABAN DRL may result in a higher risk of bleeding. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 8.2 Anticoagulants

Pharmacotherapeutic group: Antithrombotic medicines, direct factor Xa inhibitors, ATC code: B01AF02

Mechanism of action

Apixaban is an inhibitor of coagulation factor Xa (FXa). Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity.

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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.

Pharmacodynamic effects

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.

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5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of apixaban is approximately 50 % for doses up to 10 mg. Apixaban is rapidly 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.

Distribution

Plasma protein binding in humans is approximately 87 %. The volume of distribution (V_{ss}) 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 to 80 mL/min), moderate (creatinine clearance 30 to 50

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mL/min) and severe (creatinine clearance 15 to 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.

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.

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 and healthy subjects. No dose adjustment is required in patients with mild or moderate hepatic impairment. However, given the limited number of subjects studied, caution is advised when using APIXABAN DRL in this population.

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 C_{max} .

Gender

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

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 to 50 mg). The relationship between apixaban plasma concentration and anti-Factor Xa

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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

Tablet core:

Anhydrous lactose

Croscarmellose sodium

Isopropyl Alcohol

Hypromellose 5 CPS (Methocel E5 Premium)

Magnesium stearate

Methylene Chloride

Microcrystalline cellulose

Sodium lauryl sulphate

Film coat:

Opadry II White 32K580000:

Lactose Monohydrate

HPMC 2910/Hypromellose 15 mPas

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

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6.4 Special precautions for storage

Store at or below 25 °C.

Keep the container tightly closed.

6.5 Nature and contents of container

APIXABAN 2,5 DRL: HDPE bottles containing pack sizes of 60's or 180's.

APIXABAN 5 DRL: HDPE bottles containing pack sizes of 60's or 180's.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

APIXABAN 2,5 DRL: 56/8.2/0106

APIXABAN 5 DRL: 56/8.2/0107

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 October 2023