SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

APIXABAN 2,5 mg Pfizer Film-coated tablets

APIXABAN 5 mg Pfizer Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (anhydrous lactose and lactose monohydrate).

Excipients with known effect

Each APIXABAN 2,5 mg Pfizer tablet contains 50,25 mg anhydrous lactose and the film coat (in Opadry II) contains 31,00 % w/w lactose monohydrate.

Each APIXABAN 5 mg Pfizer tablet contains 100,50 mg anhydrous lactose and the film coat (in Opadry II) contains 31,00 % w/w lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

APIXABAN 2,5 mg Pfizer: Yellow, round, biconvex film-coated tablets with “893” debossed on one side and “2½” on the other side.

Tablet dimension: round tablet with a diameter of 5,95 mm (15/64”), approximate thickness: 2,7 mm.

APIXABAN 5 mg Pfizer: Pink, oval shaped, biconvex film-coated tablets with “894” debossed on one side and “5” on the other side.

Tablet dimension: oval tablet with 9,73 x 5,16 mm (0,383” x 0,203”), approximate thickness: 3,8 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prevention of VTE: elective hip or knee replacement surgery

APIXABAN BMS 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 BMS 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.

Treatment of VTE

APIXABAN BMS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE.

4.2 Posology and method of administration

APIXABAN BMS can be taken with or without food.

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

Posology

Recommended dosage

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of APIXABAN BMS 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 BMS 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 BMS is 2,5 mg twice daily.

Treatment of DVT and PE

The recommended dose of APIXABAN BMS is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Prevention of recurrent DVT and PE

The recommended dose of APIXABAN BMS is 2,5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.

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, *Recommended dosage, Age, body weight, serum creatinine.*

Treatment of VTE

No dose adjustment required (see section 5.2).

Converting from or to parenteral anticoagulants

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

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

Patients undergoing cardioversion

APIXABAN BMS 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 5 mg Pfizer 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 BMS 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 BMS 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 (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 BMS 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 - 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 BMS is not recommended in these patients (see section 5.2).

Treatment of VTE

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

Hepatic impairment

APIXABAN BMS 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, Hepatic impairment).

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

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 section 4.2, Prevention of stroke and systemic embolism: NVAF**,** *Recommended dosage, Age, body weight, serum creatinine.*

Treatment of VTE

No dose adjustment required (see section 5.2).

Paediatric population

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

Method of administration

For oral use.

For patients who are unable to swallow whole tablets, APIXABAN BMS tablets may be crushed and suspended in water, 5 % dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally (see section 5.2). Alternatively, APIXABAN BMS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube (see section 5.2).

Crushed APIXABAN BMS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

4.3 Contraindications

- Hypersensitivity to the active substance (apixaban) or to any of the excipients of APIXABAN BMS (listed in section 6.1)
- Clinically significant active bleeding
- APIXABAN BMS is not recommended in patients with severe renal disease (CrCl < 15 mL/min)
- APIXABAN BMS is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- APIXABAN BMS 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 BMS are to be carefully observed for signs of bleeding. APIXABAN BMS 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 BMS 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 prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Reversal of APIXABAN BMS 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 no clinical experience with the use of 4-factor PCC medicines to reverse bleeding in individuals who have received APIXABAN BMS. Currently there is no experience with the use of recombinant factor VIIa in individuals receiving APIXABAN BMS. Standard anticoagulation tests cannot be used to monitor APIXABAN BMS (see section 4.5).

Interaction with other medicines affecting haemostasis

The concomitant use of APIXABAN BMS 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 BMS following surgery (see section 4.5).

In patients with atrial fibrillation and a condition that warrants chronic use of aspirin, APIXABAN BMS 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 BMS 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 BMS have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of APIXABAN BMS 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 BMS in patients with APS, is inconclusive/incomplete. There is some evidence that treatment with APIXABAN BMS 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 BMS 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 BMS

Discontinue APIXABAN BMS, in the presence of active bleeding, elective surgery, or invasive procedures that place patients at an increased risk of haemorrhage. Restart APIXABAN BMS therapy 12 - 24 hours after the danger of 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, such as APIXABAN BMS, 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 procedure is planned, APIXABAN BMS 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 BMS. 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.

Acute PE in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy

Treatment of VTE

Initiation of APIXABAN BMS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with haemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

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

APIXABAN BMS 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 BMS exposure by 2-fold (see section 4.5).

Interaction with strong inducers of both CYP3A4 and P-gp

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

For the treatment of DVT or PE, APIXABAN BMS 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 BMS with strong inducers of both CYP3A4 and P-gp (see section 4.5).

Hip fracture surgery

APIXABAN BMS has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, APIXABAN BMS 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 BMS (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 BMS 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 BMS is not recommended in these patients (see section 4.2, Renal impairment, section 5.2, Renal impairment and section 4.3).

Prevention of stroke and systemic embolism: NVAF

APIXABAN BMS has not been studied in patients undergoing dialysis and is not recommended in these patients (see section 5.2).

Treatment of VTE

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

Hepatic impairment

APIXABAN BMS is not recommended in patients with severe hepatic impairment (see section 5.2, Hepatic impairment and section 4.3).

APIXABAN BMS may be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see section 4.2, Hepatic impairment and section 5.2, Hepatic impairment).

Lactose intolerance

APIXABAN BMS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on APIXABAN BMS

Inhibitors of CYP3A4 and P-gp

Co-administration of APIXABAN BMS 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 BMS AUC and a 1,6-fold increase in mean APIXABAN BMS C_{max} (see section 4.4, Interaction with inhibitors of both Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)).

The dose of APIXABAN BMS 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., diltiazem, naproxen, clarithromycin, amiodarone, verapamil, quinidine) are expected to increase APIXABAN BMS plasma concentration to a lesser extent. No dose adjustment for APIXABAN BMS is required when co-administered with medicines that are not strong inhibitors of both CYP3A4 and P-gp. 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 BMS 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 BMS 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 BMS AUC and C_{max} respectively.

Inducers of CYP3A4 and P-gp

Co-administration of APIXABAN BMS with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54 % and 42 % decrease in mean APIXABAN BMS AUC and C_{max}, respectively. The concomitant use of APIXABAN BMS with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital (phenobarbitone) or St. John's Wort) may also lead to reduced APIXABAN BMS plasma concentrations. No dose adjustment for APIXABAN BMS is required during concomitant therapy with such medicines, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution (see section 4.4, Interaction with strong inducers of both CYP3A4 and P-gp).

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 the 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 BMS (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 BMS was co-administered with aspirin 325 mg once a day.

APIXABAN BMS co-administered with clopidogrel (75 mg once daily) or with the combination of clopidogrel 75 mg and aspirin 162 mg once daily or with prasugrel (60 mg followed by 10 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 medicines without APIXABAN BMS. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of APIXABAN BMS alone. However, the co-administration of APIXABAN BMS 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 BMS AUC and C_{max}, in healthy subjects, respectively. Corresponding increases in clotting tests were observed for APIXABAN BMS. No clinically relevant prolongation of bleeding time was observed after concomitant administration of APIXABAN BMS and naproxen.

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

Medicines associated with serious bleeding are not recommended concomitantly with APIXABAN BMS, 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 medicines, 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 medicines affecting haemostasis).

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when APIXABAN BMS was co-administered with atenolol or famotidine. Co-administration of APIXABAN BMS 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of APIXABAN BMS. Following administration of the two medicines together, mean APIXABAN BMS AUC and C_{max} were 15 % and 18 % lower than when administered alone. The administration of APIXABAN BMS 10 mg with famotidine 40 mg had no effect on APIXABAN BMS AUC or C_{max}.

Effect of APIXABAN BMS on other medicines

In vitro APIXABAN BMS 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 BMS did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, APIXABAN BMS is not expected to alter the metabolic clearance of co-administered medicines that are metabolised by these enzymes. APIXABAN BMS is not a significant inhibitor of P-gp.

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

Digoxin

Co-administration of APIXABAN BMS (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 BMS does not inhibit P-gp mediated substrate transport.

Naproxen

Co-administration of single doses of APIXABAN BMS (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 BMS (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 BMS is not recommended during pregnancy. Treatment may increase the risk of haemorrhage during pregnancy and delivery.

Breastfeeding

It is unknown whether APIXABAN BMS or its metabolites are excreted in human milk. In rat milk, a high milk to maternal plasma ratio (C_{max} about 8, AUC about 30) was found, possibly due to active transport into the milk. A risk to newborns and infants cannot be excluded.

Women taking APIXABAN BMS should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of APIXABAN BMS has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1,7 years and 221 days respectively.

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

In the VTEp studies, in total, 11 % of the patients treated with APIXABAN 2,5 mg Pfizer twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with APIXABAN BMS was 10 % in the APIXABAN BMS vs enoxaparin studies.

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with APIXABAN BMS was 24,3 % in the APIXABAN BMS vs warfarin study and 9,6 % in the APIXABAN BMS vs acetylsalicylic acid study. In the APIXABAN BMS vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with APIXABAN BMS was 0,76 %/year. The incidence of ISTH major intraocular bleeding with APIXABAN BMS was 0,18 %/year.

In the VTEt studies, the overall incidence of adverse reactions related to bleeding with APIXABAN BMS was 15,6 % in the APIXABAN BMS vs enoxaparin/warfarin study and 13,3 % in the APIXABAN BMS vs placebo study.

Tabulated list of adverse reactions

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

Table 1: Tabulated adverse reactions

System organ class	Prevention of VTE in adult patients who have undergone elective hip or	Prevention of stroke and systemic embolism in adult patients with	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)

	knee replacement surgery (VTEp)	NVAF, with one or more risk factors (NVAF)	
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
Immune system disorders			
Hypersensitivity, allergic oedema and anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Angioedema	Not known	Not known	Not known
Nervous system disorders			
Brain haemorrhage†	Not known	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon

Intra-abdominal haemorrhage	Not known	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not known	Rare	Rare
Gastrointestinal disorders			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage	Not known	Uncommon	Uncommon
Mouth haemorrhage	Not known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not known	Rare	Not known
Hepatobiliary disorders			
Liver function test abnormal, increased asparate aminotransferase, increased blood	Uncommon	Uncommon	Uncommon

alkaline phosphatase, increased blood bilirubin			
Increased gamma-glutamyltransferase	Uncommon	Common	Common
Increased alanine aminotransferase	Uncommon	Uncommon	Common
Skin and subcutaneous tissue disorders			
Skin rash	Not known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Rare	Uncommon
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
General disorders and administration site conditions			
Application site bleeding	Not known	Uncommon	Uncommon
Investigations			
Positive occult blood	Not known	Uncommon	Uncommon

Injury, poisoning and procedural complications			
Contusion	Common	Common	Common
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	Uncommon	Uncommon	Uncommon
Traumatic haemorrhage	Not known	Uncommon	Uncommon

* There were no occurrences of generalised 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 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 BMS. Overdose of APIXABAN BMS 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 BMS reduced mean APIXABAN BMS AUC by 50 % and 27 %, respectively, and had no impact on C_{max}. Mean half-life of APIXABAN BMS decreased from 13,4 hours when APIXABAN BMS was administered alone to 5,3 hours and 4,9 hours, respectively, when activated charcoal was administered 2 and 6 hours after APIXABAN BMS. Thus, administration of activated charcoal may be useful in the management of APIXABAN BMS overdose or accidental ingestion.

Haemodialysis is unlikely to be an effective means of managing APIXABAN BMS 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 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 PT, INR and 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 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 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).

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, Prevention of stroke and systemic embolism: NVAF).

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.

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: nonvalvular atrial fibrillation (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, 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 BMS in this population (see section 4.2, Hepatic impairment and section 4.4, Hepatic impairment).

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32 % higher. (See section 4.2, Prevention of stroke and systemic embolism: NVAF).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

anhydrous lactose

croscarmellose sodium

magnesium stearate

microcrystalline cellulose

sodium lauryl sulphate

Film coating

hypromellose

lactose monohydrate

titanium dioxide

triacetin

yellow iron oxide (2,5 mg tablets)

red iron oxide (5 mg tablets)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container

APIXABAN 2,5 mg Pfizer: Cartons containing clear PVC/PVDC/silver aluminium blisters of 10 film-coated tablets (1 blister of 10 film-coated tablets each), 20 film-coated tablets (2 blisters of 10 film-coated tablets

each) or 60 film-coated tablets (6 blisters of 10 film-coated tablets each).

APIXABAN 5 mg Pfizer: Cartons containing clear PVC/PVDC/silver aluminium blisters of 20 film-coated tablets (2 blisters of 10 film-coated tablets each), 60 film-coated tablets (6 blisters of 10 film-coated tablets each) or 14 film-coated tablets (1 blister of 14 film-coated tablets each) or 56 film-coated tablets (4 blisters of 14 film-coated tablets each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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8. REGISTRATION NUMBERS

APIXABAN 2,5 mg Pfizer: 47/8.2/0465

APIXABAN 5 mg Pfizer: 47/8.2/0466

9. DATE OF FIRST AUTHORISATION

20 March 2018

10. DATE OF REVISION OF THE TEXT

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Manufacturer: Bristol-Myers Squibb Manufacturing Company, Humacao, Puerto Rico