Professional Information for CLOTIXAR

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

CLOTIXAR 2,5 mg film-coated tablets

CLOTIXAR 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

CLOTIXAR 5: Each film-coated tablet contains 5 mg apixaban.

Excipients with known effect:

Contains sugar.

CLOTIXAR 2,5: Each film-coated tablet contains 58,128 mg lactose.

CLOTIXAR 5: Each film-coated tablet contains 113,064 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

CLOTIXAR 2,5: White to off-white coloured, round shaped, film-coated tablets, debossed with "1181" on one side and plain on the other side.

CLOTIXAR 5: Beige coloured, oval shaped, film-coated tablets, debossed with "1182" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

CLOTIXAR 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)

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

Treatment of VTE

CLOTIXAR 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

Posology

Prevention of VTE: elective hip or knee replacement surgery

The recommended dose of CLOTIXAR 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 CLOTIXAR 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 mmol/L), the recommended dose of CLOTIXAR is 2,5 mg twice daily.

Treatment of DVT and PE

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

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 to moderate or severe renal impairment (creatinine clearance 15 – 29 mL/min) (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, CLOTIXAR is not recommended in these patients (see sections 4.4 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 – 29 mL/min, except as described under **Posology and method of administration, *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, CLOTIXAR is not recommended in these patients.

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, CLOTIXAR is not

recommended in these patients (see section 5.2).

Hepatic impairment

CLOTIXAR 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 and 5.2).

CLOTIXAR is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

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 **Posology and method of administration, *Prevention of stroke and systemic embolism: NVAF***.

Treatment of VTE

No dose adjustment required (see section 5.2).

Paediatric and adolescent patients

The efficacy and safety of CLOTIXAR in children below the age of 18 years have not been established. No data are available.

Elderly patients

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 **Posology and method of administration, *Prevention of stroke and systemic embolism: NVAF***.

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 CLOTIXAR (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 CLOTIXAR, discontinue warfarin or other VKA therapy and start CLOTIXAR when the international normalised ration (INR) is below 2,0.

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

Surgery and invasive procedures

CLOTIXAR 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.

Method of administration

Oral use.

CLOTIXAR should be swallowed with water and can be taken with or without food.

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

4.3 Contraindications

- Hypersensitivity to apixaban or to any of the excipients of CLOTIXAR listed in section 6.1.
- Active clinically significant bleeding.
- CLOTIXAR is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- CLOTIXAR is not recommended in patients with severe renal disease (CrCl < 15 mL/min).
- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- CLOTIXAR should not be administered with antiplatelet medicines other than aspirin (see section 4.4). Concomitant treatment with any other anticoagulant medicine, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2), 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 sections 4.4 and 4.5).
- 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 CLOTIXAR 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. CLOTIXAR 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 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 CLOTIXAR. Standard anticoagulation test cannot be used to monitor CLOTIXAR (see section 4.5).

There is no reversal medicine for CLOTIXAR.

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 CLOTIXAR 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 nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin.

Following surgery, other platelet aggregation inhibitors or other antithrombotic medicines are not recommended concomitantly with CLOTIXAR (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 CLOTIXAR.

Use of thrombolytic medicines for the treatment of acute ischaemic stroke

There is very limited experience with the use of thrombolytic medicines for the treatment of acute ischaemic stroke in patients administered CLOTIXAR.

Patients with prosthetic heart valves

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

Patients with antiphospholipid syndrome

Direct acting oral anticoagulants (DOACs), including CLOTIXAR, 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 (see section 4.3).

Surgery and invasive procedures

CLOTIXAR 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.

CLOTIXAR 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.

CLOTIXAR 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, CLOTIXAR treatment does not need to be interrupted (see sections 4.2, 4.3 and 4.5).

Temporary discontinuation

Discontinuing anticoagulants, including CLOTIXAR, 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 CLOTIXAR must be temporarily discontinued for any reason, therapy should be restarted as soon as possible (12 – 24 hours after the danger of haemorrhage has ceased).

Haemodynamically unstable pulmonary embolism (PE) patients or patients who require thrombolysis or pulmonary embolectomy

CLOTIXAR 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 CLOTIXAR in the treatment of deep vein thrombosis (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 treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), CLOTIXAR 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 mmol/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, CLOTIXAR is not recommended (see sections 4.2 and 5.2).

Elderly patients

Increasing age may increase haemorrhagic risk (see section 5.2).
Also, the co-administration of CLOTIXAR with aspirin in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Paediatric patients

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

Body weight

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

Patients with hepatic impairment

CLOTIXAR 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 alanine aminotransferase (ALT) / aspartate transaminase (AST) > 2 x ULN or total bilirubin > 1,5 x the upper limit of normal (ULN) were excluded in clinical trials. Therefore, CLOTIXAR should be used cautiously in this population (see section 5.2). Prior to

initiating CLOTIXAR, liver function testing should be performed.

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

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

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5):

- for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, CLOTIXAR should be used with caution;
- for the treatment of DVT and treatment of PE, CLOTIXAR should not be used since efficacy may be compromised.

Spinal/epidural anaesthesia or puncture

Prevention of VTE: elective hip or knee replacement surgery

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines, such as CLOTIXAR, for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which

can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. When an indwelling epidural or intrathecal catheter is planned, CLOTIXAR should be stopped 48 hours beforehand. Indwelling epidural or intrathecal catheters must be removed at least 6 hours prior to the first dose of CLOTIXAR. 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 CLOTIXAR 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.

Hip fracture surgery

The safety and efficacy of CLOTIXAR in patients undergoing hip fracture surgery have not been evaluated in clinical trials. Therefore, CLOTIXAR 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

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

4.5 Interaction with other medicines and other forms of interaction

Inhibitors of CYP3A4 and P-gp

Co-administration of CLOTIXAR 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 area under the curve (AUC) and a 1,6-fold increase in mean apixaban C_{max}.

The dose of CLOTIXAR must not exceed 2,5 mg twice daily when used with these medicines.

The use of CLOTIXAR 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 human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir) (see section 4.4).

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 plasma concentration to a lesser extent. No dose adjustment for CLOTIXAR is required when co-administered 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 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.

Inducers of CYP3A4 and P-gp

Co-administration of CLOTIXAR 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 CLOTIXAR with other strong CYP3A4 and P-gp inducers (e.g. phenytoin,

carbamazepine, phenobarbital or St John's wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for CLOTIXAR is required during concomitant therapy with such medicines, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp, CLOTIXAR should be used with caution for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE. CLOTIXAR 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 of CLOTIXAR 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 CLOTIXAR (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

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

CLOTIXAR co-administered with clopidogrel (75 mg once a day) 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) did not show a relevant increase in template bleeding time, or further inhibition of platelet aggregation, compared to administration of the antiplatelet medicines without CLOTIXAR. Increases in clotting tests (PT, INR and aPTT) were consistent with the effects of CLOTIXAR 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 C_{max}, 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 CLOTIXAR and naproxen.

Despite these findings, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet medicines are co-administered with CLOTIXAR. CLOTIXAR should be used with caution when co-administered with SSRIs/SNRIs or NSAIDs (including aspirin) because these medicines typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, aspirin and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).

Medicines associated with serious bleeding are not recommended concomitantly with CLOTIXAR, such as thrombolytic medicines, GPIIb/IIIa receptor antagonists, thienopyridines (e.g. clopidogrel), dipyridamole, dextran and sulfinpyrazone.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when CLOTIXAR 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 CLOTIXAR. 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 CLOTIXAR 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.

Effect of apixaban on other medicines

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

CLOTIXAR is not a significant inhibitor of P-gp.

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

Digoxin

Co-administration of CLOTIXAR (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, CLOTIXAR does not inhibit P-gp mediated substrate transport.

Naproxen

Co-administration of single doses of CLOTIXAR (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol

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

Activated charcoal

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of CLOTIXAR in pregnant women. Treatment may increase the risk of haemorrhage during pregnancy and delivery. CLOTIXAR is not recommended during pregnancy.

Lactation

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

CLOTIXAR is not recommended in mothers who are breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Table 1: Adverse reaction profile and frequencies by indication

System organ class	***Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)***	***Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)***	***Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)***
Blood and lymphatic system disorders			
Anaemia	*Frequent*	*Frequent*	*Frequent*
Thrombocytopenia	*Less frequent*	*Less frequent*	*Frequent*
Immune system disorders			
Hypersensitivity, allergic oedema, 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			
Ocular 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 (including 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, aspartate 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*
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*

* The term “brain haemorrhage” encompasses all intracranial or intraspinal haemorrhages (i.e. haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).
The use of CLOTIXAR may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in post-haemorrhagic 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 CLOTIXAR is important. It allows continued monitoring of the benefit/risk balance of CLOTIXAR. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP

(Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Overdose of CLOTIXAR may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated.

Administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban, as in CLOTIXAR, reduced mean apixaban AUC by 50 % and 27 %, respectively, and had no impact on C_{max}. Mean half-life of apixaban decreased from 13,4 hours when apixaban was administered alone, to 5,3 hours and 4,9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of CLOTIXAR overdose or accidental ingestion. Haemodialysis is unlikely to be an effective means of managing CLOTIXAR overdose.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors.

ATC code: B01AF02.

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site 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.

Pharmacodynamic effects

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic 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 Factor Xa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Data from clinical trials are only available for the Rotachrom® Heparin chromogenic assay. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is approximately linear over a wide dose range of apixaban.

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.

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 approximately 20 % CV and approximately 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 C_{max} 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 5 % dextrose in water 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 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).

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 (see section 4.2, Prevention of stroke and systemic embolism: nonvalvular atrial fibrillation [NVAF]).

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 hepatic impairment, Child-Pugh A, and moderate hepatic impairment, Child-Pugh B, to 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. No dose adjustment is required in patients with

mild to moderate hepatic impairment. However, given the limited number of subjects studied, caution is advised when using CLOTIXAR in this population (see sections 4.2 and 4.4).

Elderly patients

Elderly patients (above 65 years of age) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32 % higher and no difference in C_{max} (see section 4.2).

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

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0,5 – 50 mg). The relationship between apixaban plasma concentration and anti-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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-fetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies little

to no increase of bleeding tendency was found.

However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium (E468)

Hypromellose (E464)

Lactose anhydrous

Magnesium stearate (E572)

Microcrystalline cellulose (E460)

Stearic acid (E570)

Tetrahydrofuran.

Film-coating:

CLOTIXAR 2,5:

Opadry White (containing hypromellose [E464], lactose monohydrate, titanium dioxide [E171] and triacetin)

CLOTIXAR 5:

Opadry Beige (containing hypromellose [E464], lactose monohydrate, titanium dioxide [E171], triacetin, iron oxide yellow [E172] and iron oxide red [E172]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear transparent PVC/PVDC/aluminium blister strips containing 10 tablets, packed into an outer container.

Pack sizes: 30 or 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

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Building B, Ground Floor

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8. REGISTRATION NUMBERS

CLOTIXAR 2,5: 55/8.2/0055.053

CLOTIXAR 5: 55/8.2/0056.054

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

9 February 2021

10. DATE OF REVISION OF THE TEXT

18 December 2025