PRACTICAL GUIDE

LIXIANA® (edoxaban)

For clinical data and prescriber resources please visit www.lixiana.com

Please refer to the Prescribing Information on the back cover.

Daiichi-Sankyo

once-daily Lixiana® edoxaban

OVERVIEW

THIS GUIDE IS SPECIFICALLY FOR PRESCRIBERS IN RELATION TO THE USE OF LIXIANA® (EDOXABAN)

It includes information on the following:

- Indications
- Summary of efficacy and safety data from NVAF and VTE pivotal studies
- Dosing recommendations and dose reduction
- Information on switching patients to or from LIXIANA®
- Contraindications
- Special patient populations
- Temporary discontinuation
- Perioperative management
- Overdose
- Management of bleeding complications
- Coagulation testing

Please consult the Summary of Product Characteristics (SmPC) for full prescribing information.

ONCE-DAILY LIXIANA® FOR YOUR ELIGIBLE PATIENTS WITH NVAF

INDICATIONS[1]

LIXIANA® is indicated for:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

SIMPLE AND CONVENIENT FOR PATIENTS AND PRESCRIBERS[5]

- Once-daily dosing, with or without food

EFFICACY AND SAFETY IN NVAF

PROVEN EFFICACY IN PREVENTING STROKE AND SEE IN NVAF PATIENTS – COMPARABLE TO WELL-CONTROLLED WARFARIN

- LIXIANA® was comparable to well-controlled warfarin in the prevention of stroke and SEE in the modified intention-to-treat population (primary efficacy endpoint)[2]
- In NVAF patients with high CrCl, there is a trend towards decreasing efficacy with increasing CrCl for edoxaban vs well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation

STROKE/SEE IN THE INTENTION-TO-TREAT POPULATION DURING THE OVERALL STUDY PERIOD[2]

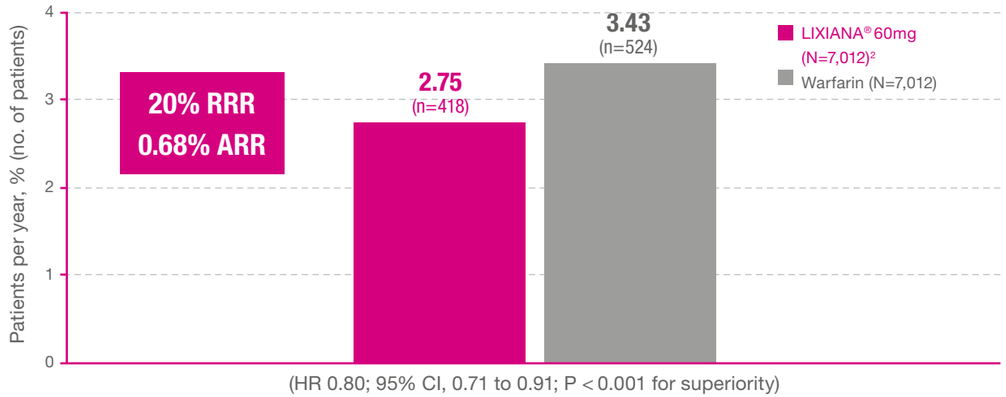
Numbers presented are from the intention-to-treat population with 97.5% CI and P values for superiority.
Noninferiority was tested in the modified intention-to-treat on-treatment population who received at least one dose of study drug.

- Patients on the 30 mg reduced dose achieved efficacy consistent with overall trial results[3]

SEE, systemic embolic events; HR, hazard ratio; CI, confidence interval

SUPERIOR REDUCTION IN MAJOR BLEEDING IN NVAF PATIENTS VS. WELL-CONTROLLED WARFARIN

ANNUAL RATE OF MAJOR BLEEDING EVENTS (PRIMARY SAFETY ENDPOINT) IN THE SAFETY ON-TREATMENT POPULATION[2]



- Patients on the 30 mg reduced dose achieved a reduction in major bleeding consistent with overall trial results[3]

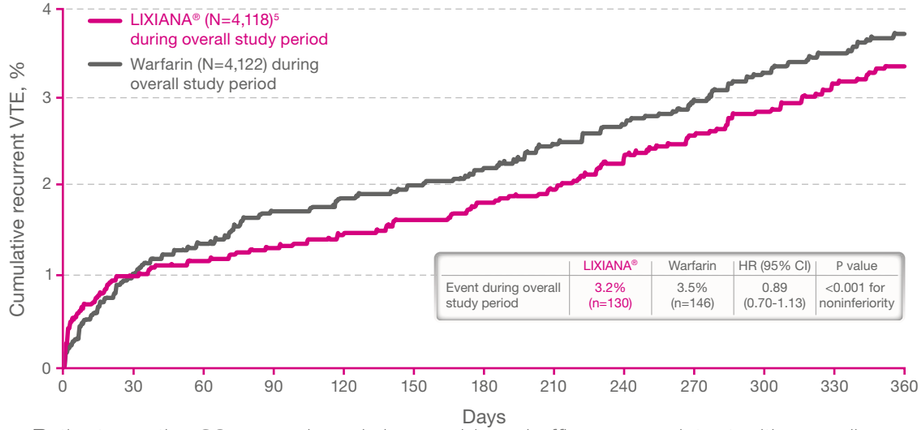
The primary safety endpoint was the incidence of adjudicated major bleeding,[4] defined by the International Society on Thrombosis and Haemostasis (ISTH) as (i) fatal bleeding; and/or (ii) symptomatic bleeding in critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome, and/or (iii) bleeding causing a fall in haemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[4]

RRR, relative risk reduction; ARR, absolute risk reduction

EFFICACY AND SAFETY IN DVT AND PE

PROVEN EFFICACY IN THE TREATMENT AND PREVENTION OF RECURRENT VTE – COMPARABLE TO WELL-CONTROLLED WARFARIN

FIRST RECURRENT VTE EVENTS (PRIMARY EFFICACY ENDPOINT) DURING OVERALL STUDY AND ON-TREATMENT PERIODS[5]



	LIXIANA®	Warfarin	HR (95% CI)	P value
Event during overall study period	3.2% (n=130)	3.5% (n=146)	0.89 (0.70-1.13)	<0.001 for noninferiority

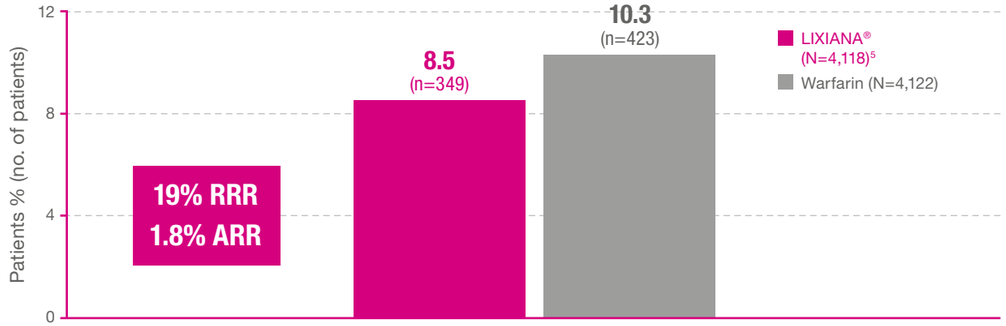
- Patients on the 30 mg reduced dose achieved efficacy consistent with overall trial results[5]
- In NVAF patients with high CrCl, there is a trend towards decreasing efficacy with increasing CrCl for edoxaban vs well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation

* The overall study period included the period of randomisation through to the end of 12 months or study closure[5]

A Includes patients taking LIXIANA® 60mg and those dose-reduced to 30 mg.

SUPERIOR REDUCTION IN CLINICALLY RELEVANT BLEEDING IN VTE PATIENTS VS. WELL-CONTROLLED WARFARIN

COMPOSITE OF MAJOR AND CLINICALLY RELEVANT NONMAJOR BLEEDING EVENTS (PRIMARY SAFETY ENDPOINT) DURING ON-TREATMENT PERIOD[5]



(HR 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority)

- Patients on the 30 mg reduced dose achieved a reduction in clinically relevant bleeding consistent with overall trial results[5]

A Includes patients taking LIXIANA® 60 mg and those dose-reduced to 30 mg.

The primary safety endpoint was a composite of major and clinically relevant nonmajor bleeding,[9] as defined by the International Society on Thrombosis and Haemostasis (ISTH). Major bleeding was defined as overt bleeding associated with a decrease in haemoglobin of 2.0 g/L or more, or requiring a transfusion of 2 or more units of blood, occurring in a critical site or contributing to death.[4] Clinically relevant non major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with other discomfort such as pain, or impairment of daily life activities.[6]

DOSING

THE RECOMMENDED DOSE OF LIXIANA® IS 60 MG IN A ONCE-DAILY TABLET[1]

It can be taken with water, with or without food. To aid compliance, patients should be encouraged to take their dose at the same time every day.

Treatment with LIXIANA® in patients with NVAF should be continued long term.

The duration of treatment for VTE and prevention of recurrent VTE should be individualised after assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

RECOMMENDED DOSE

60 mg
Tablet actual size

INITIATING TREATMENT[1]

For the treatment of VTE, patients should receive an initial course of heparin for at least 5 days prior to treatment with LIXIANA®. This is not required for the initiation of LIXIANA® in patients with NVAF for the prevention of stroke and systemic embolism.

Renal function (CrCl) and liver function should be assessed in all patients prior to LIXIANA® initiation. In NVAF patients with high CrCl, there is a trend towards decreasing efficacy with increasing CrCl for edoxaban vs well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation.

Information on switching patients to LIXIANA® from other treatments can be found on pages 10 to 13.

DOSE REDUCTION[1]

A dose of 30 mg once daily is required for certain patients who fall into one or more of the following subgroups.

These are:

MODERATE OR SEVERE RENAL IMPAIRMENT (CREATININE CLEARANCE [CRCL] 15–50 ML/MIN)

BODY WEIGHT ≤60 KG

CONCOMITANT USE OF THE P-GP INHIBITORS DRONEDARONE, CICLOSPORIN, ERYTHROMYCIN, KETOCONAZOLE

30 mg
Tablet actual size

In this case, patients should take one 30 mg tablet at the same time every day, with or without food.

MISSED DOSE[1]

If a patient misses a dose of LIXIANA® he/she should take it immediately and then continue the following day with the once-daily intake as recommended.

The patient should not take double the prescribed dose on the same day to make up for a missed dose.

SWITCHING TO AND FROM LIXIANA®

Switching patients to or from treatment with LIXIANA® is the same for both the VTE and NVAF indications. It should be noted that once a patient is switched to treatment with LIXIANA®, International Normalised Ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) are not useful measurements for anticoagulation effect.[1]

FROM NON-VKA ORAL ANTICOAGULANTS (NOAC) TO LIXIANA[1]

Discontinue the NOAC and start LIXIANA® at the time of the next non-VKA dose.

FROM LIXIANA® TO NOAC[1]

Discontinue LIXIANA® and start the NOAC at the time of the next scheduled dose of LIXIANA®.

FROM VKA THERAPY TO LIXIANA[1]

When converting patients from VKA therapy to LIXIANA®, discontinue warfarin or other VKA therapy and start LIXIANA® treatment when the INR is ≤2.5.

VKA, vitamin K antagonist

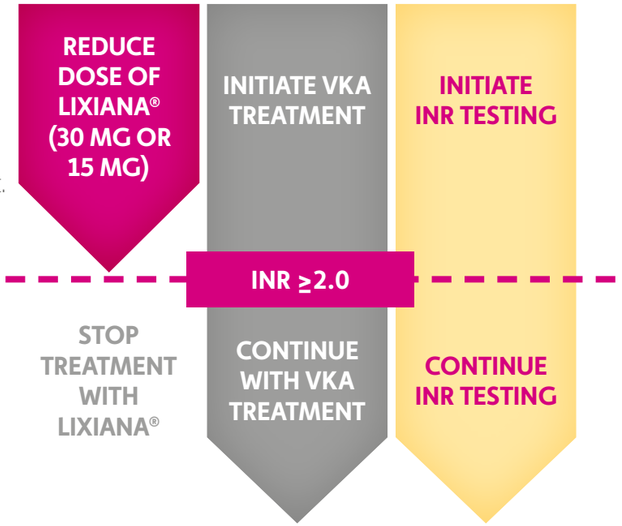
FROM LIXIANA® TO VKA THERAPY[1]

ORAL OPTION

There is a potential for inadequate anticoagulation during the transition from LIXIANA® to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. For patients currently on a 60 mg dose, administer a LIXIANA® dose of 30 mg once daily together with an appropriate VKA dose. For patients currently on a 30 mg dose, administer a LIXIANA® dose of 15 mg once daily together with an appropriate VKA dose.

Patients should not take a loading dose of VKA in order to promptly achieve a stable INR between 2 and 3. It is recommended to take into account the maintenance dose of VKA and if the patient was previously taking a VKA or to use valid INR driven VKA treatment algorithm, in accordance with local practice.

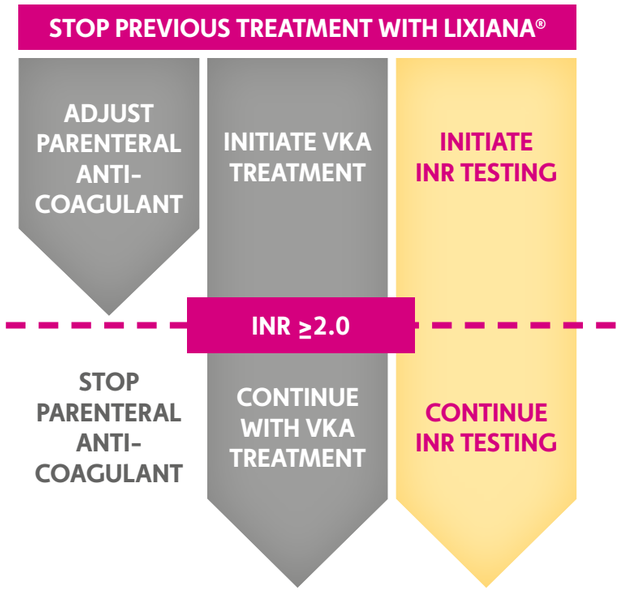
Once an INR ≥2.0 is achieved, LIXIANA® should be discontinued. Most patients (85%) should be able to achieve an INR ≥2.0 within 14 days of concomitant



administration of LIXIANA® and VKA. After 14 days it is recommended that LIXIANA® is discontinued and the VKA continued to be titrated to achieve an INR between 2 and 3. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least 3 times just prior to taking the daily dose of Lixiana to minimise the influence of Lixiana on INR measurements. Concomitant Lixiana and VKA can increase the INR post Lixiana dose by up to 46 %.

PARENTERAL ROUTE[1]

Discontinue LIXIANA® treatment and administer a parenteral anticoagulant and VKA treatment at the time of the next scheduled LIXIANA® dose. Once a stable INR of ≥2.0 is achieved, the parenteral anticoagulant should be discontinued and the VKA continued.



FROM PARENTERAL ANTICOAGULANT TO LIXIANA[1]

LIXIANA® should not be administered simultaneously with a parenteral anticoagulant.

Patients on continuously administered parenteral drug such as intravenous (IV) unfractionated heparin:

DISCONTINUE INFUSION → **WAIT 4 HOURS** → **START LIXIANA® ONCE DAILY**

Patients on subcutaneous anticoagulant (low molecular weight heparin (LMWH), e.g. fondaparinux):

DISCONTINUE SUBCUTANEOUS ANTICOAGULANT → **BEGIN LIXIANA® TREATMENT AT THE TIME OF NEXT SCHEDULED DOSE OF PREVIOUS TREATMENT**

FROM LIXIANA® TO PARENTERAL ANTICOAGULANT[1]

LIXIANA® should not be administered simultaneously with a parenteral anticoagulant.

Discontinue LIXIANA® and start the parenteral anticoagulant at the time of the next scheduled dose of LIXIANA®.

CONTRAINDICATIONS

As an anticoagulant, LIXIANA® may increase the risk of bleeding. Therefore, patients prescribed LIXIANA® should be carefully observed for signs of bleeding.[1]

LIXIANA® is contraindicated in the following patients:[1]
• Those with hypersensitivity to the active substance or to any of the excipients
• Those with clinically significant active bleeding
• Those with a lesion or condition at significant risk of major bleeding such as: – Current or recent gastrointestinal (GI) ulceration – Malignant neoplasms at high risk of bleeding – Recent brain or spinal injury or surgery – Recent ophthalmic surgery – Recent intracranial haemorrhage – Suspected or diagnosed oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
• Those with hepatic disease associated with coagulopathy and clinically relevant bleeding risk
• Those on concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparin (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban, etc.) except under the circumstances of switching therapy to or from LIXIANA® or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
• LIXIANA® is contraindicated during pregnancy and women of child-bearing potential should avoid becoming pregnant during treatment. As LIXIANA® is also contraindicated during breastfeeding, it should be decided whether to cease therapy or to discontinue breastfeeding
• Those with uncontrolled severe hypertension

SPECIAL PATIENT POPULATIONS

Several groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Any treatment decision must be based on careful assessment of the treatment benefit against risk of bleeding.[1]

Prior to initiation of LIXIANA® and when clinically indicated, renal function testing (CrCl) should be performed

Patients with renal impairment[1]	
End stage renal disease: dialysis, renal failure (CrCl <15 ml/min)	Not recommended
Moderate or severe renal impairment (CrCl 15–50 ml/min)	Dose reduction to 30 mg once daily (OD) (see Dose reduction section on page 9)
Mild renal impairment (CrCl >50–80 ml/min)	No dose reduction required – 60 mg OD

Renal function in NVAF	
Patients with NVAF and high creatinine clearance	There is a trend towards decreasing efficacy with increasing CrCl for edoxaban vs well-managed wararin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation

Patients with hepatic impairment[1]	
Hepatic disease associated with coagulopathy and clinically relevant bleeding	Contraindicated
Mild or moderate hepatic impairment	No dose reduction required – 60 mg OD; use with caution
Severe hepatic impairment	Not recommended
Elevated liver enzymes ALT/AST >2x ULN or total bilirubin ≥1.5x ULN	Use with caution

Prior to initiation and during long term treatment (>1 year) with LIXIANA®, liver function testing should be performed.

Patients receiving concomitant treatment[1]	
P-gp inhibitors: dronedarone, ciclosporin, erythromycin, ketoconazole	Dose reduction to 30 mg OD (see Dose reduction section page 9)
Amiodarone, quinidine, or verapamil	No dose reduction required – 60 mg OD
P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitol or St Johns Wort)	Use with caution
P-gp substrates (digoxin)	No dose modification – 60 mg OD
Medication affecting haemostasis such as NSAIDs, aspirin/acetylsalicylic acid (ASA), or platelet aggregation inhibitors	Not recommended. LIXIANA® can be coadministered with low dose ASA (≤100 mg/day)
Chronic use of NSAIDs	Not recommended
Selective serotonin reuptake inhibitors (SSRIs)/Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Possibility of increased risk of bleeding

TEMPORARY DISCONTINUATION[1]

Breaks in therapy should be avoided wherever possible. However, in an instance where a temporary discontinuation is unavoidable (e.g. before a surgical intervention or invasive procedure), LIXIANA® should be restarted as soon as possible.

PERIOPERATIVE MANAGEMENT[1]

In situations where a patient requires a surgical intervention or invasive procedure (including tooth extraction), **LIXIANA® should be stopped as soon as possible and preferably at least 24 hours beforehand**, and appropriate caution exercised due to the increased risk of thrombosis. The half-life of LIXIANA® is 10–14 hours.

In deciding whether a procedure should be delayed until 24 hours after the last dose of LIXIANA®, the increased risk of bleeding should be weighed against the urgency of the intervention. LIXIANA® should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established, noting that the time to onset of the LIXIANA® anticoagulant therapeutic effect is 1–2 hours. If oral medicinal products cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant and then switch to oral once-daily LIXIANA®.

OVERDOSE[1]

Overdose with LIXIANA® may lead to haemorrhage. A specific antidote antagonising the pharmacodynamic effect of LIXIANA® is not available. Early administration of activated charcoal may be considered in case of LIXIANA® overdose to reduce absorption. This recommendation is based on standard treatment of drug overdose and data available with similar compounds, as the use of activated charcoal to reduce absorption of LIXIANA® has not been specifically studied in the LIXIANA® clinical programme.

MANAGEMENT OF BLEEDING COMPLICATIONS[1]

If bleeding complications are experienced, treatment should be delayed or discontinued, taking the half-life of LIXIANA® (10–14 hours) into account.

Management should be individualised according to the severity and location of the haemorrhage:

- Symptomatic treatment, such as mechanical compression, surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood product or platelets
- For life-threatening bleeding that cannot be controlled with measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of LIXIANA® 30 minutes after completing the infusion

Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving LIXIANA®.

Haemodialysis does not significantly contribute to LIXIANA® clearance.

ROUTINE COAGULATION TESTING[1]

Treatment with LIXIANA® does not require routine clinical coagulation monitoring. As a result of Factor Xa inhibition, LIXIANA® prolongs standard clotting tests such as INR, prothrombin time (PT), or 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. These tests are therefore not recommended to assess the pharmacodynamic effects of LIXIANA®.

There are no specific blood tests or assays available for LIXIANA®.

PRESCRIBING INFORMATION

LIXIANA 60 mg / 30 mg film-coated tablets
See Lixiana Summary of Product Characteristics (SmPC) Each film-coated tablet contains 60 mg / 30 mg edoxaban (as tosilate).

List of excipients: Tablet core: Mannitol (E421), Pregelatinised starch, Crospovidone (E1202), Hydroxypropylcellulose (E463), Magnesium stearate (E470b). Film-coat: Hypromellose (E464), Macrogol (8000), Titanium dioxide (E171), Talc (E553b), Carnauba wax, Iron oxide (E172) yellow (60 mg) or red (30 mg). **Therapeutic indications/Posology and method of administration:** Lixiana is indicated in prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). The recommended dose is 60 mg edoxaban once daily. Therapy with edoxaban in NVAF patients should be continued long term. Lixiana is indicated in treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults. The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min), low body weight ≤ 60 kg, Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. A 15 mg dose is available. It is not indicated for monotherapy but should only be used for switching from edoxaban 30 mg to VKA. Patients undergoing cardioversion: Lixiana can be initiated or continued in patients who may require cardioversion. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered to be a significant risk 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. Uncontrolled severe hypertension. Concomitant treatment with any other anticoagulants e.g. UFH, LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Pregnancy and breast-feeding. **Special warnings and precautions for use:** Edoxaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Edoxaban,like other anticoagulants, is recommended to be used with caution in patients with increased risk of bleeding. Edoxaban administration should be discontinued if severe haemorrhage occurs. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available. Renal function: In patients with end stage renal disease or on dialysis, Lixiana is not recommended. In NVAF, a trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin. In patients with NVAF and high CrCl edoxaban should be used only after careful evaluation of the individual thromboembolic and bleeding risk. Hepatic impairment: Edoxaban is not recommended in patients with severe hepatic impairment. Edoxaban should be used with caution in patients with mild or moderate hepatic impairment. Edoxaban should be used with caution in patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN. Interaction with medicinal products affecting haemostasis: Concomitant use of these medicines may increase the risk of bleeding. These include ASA , P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and chronic nonsteroidal anti-inflammatory drugs (NSAIDs). Prosthetic heart valves and moderate to severe mitral stenosis: Use of edoxaban is not recommended in these patients. Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy: Edoxaban is not recommended as an alternative to UFH in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Patients with active cancer: Efficacy and safety of edoxaban in the treatment and/or prevention of VTE in patients with active cancer have not been established. Patients with antiphospholipid syndrome (APS): DOACs (Direct acting oral anticoagulants) including edoxaban are not recommended for patients with APS with a history of thrombosis, particularly high-risk patients (those who test positive for all three antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies). In patients with APS, DOACs could be associated with increased rates of recurrent thrombotic events, compared with vitamin K antagonist therapy. **Undesirable effects: The safety profile of edoxaban is based on two Phase 3 studies (21,105 patients with NVAF and 8,292 patients with VTE (DVT and PE)), and from post-authorisation experience.** Common: anaemia, epistaxis, lower gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gammaglutamyltransferase increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal, dizziness, headache, abdominal pain. Uncommon: hypersensitivity, intracranial haemorrhage (ICH), conjunctival/scleral haemorrhage, intraocular haemorrhage, other haemorrhage, haemoptysis, blood alkaline phosphatase increased, transaminases increased,, urticaria, surgical site haemorrhage, thrombocytopenia. Rare: anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Other information:** Only available on prescription. Refer to LIXIANA product information before prescribing. This medicinal product is subject to additional monitoring.
Date of last revision of the text: 24.02.2020
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References:
1. LIXIANA® Summary of Product Characteristics.
2. Giugliano RP *et al. NEJM* 2013;369(22):2093–2104.
3. Giugliano RP *et al. NEJM* 2013;369(22):2093–2104. *Supplementary information table.*
4. Schulman S and Kearon C. *J Thromb Haemost* 2005; 3(4):692–694.
5. The Hokusai-VTE Investigators. *NEJM* 2013;369(15): 1406–1415.
6. The van Gogh Investigators. *NEJM* 2007;357:1094–1104.

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