Daiichi-Sankyo

Important Risk Minimisation Information for Healthcare Professionals

# Prescriber Guide

## LIXIANA® (edoxaban)

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks, therefore it is advised to be read carefully before prescribing/dispensing the product

Healthcare professionals are asked to report any suspected adverse reactions. See page 16 for information on how to report adverse reactions.

# OVERVIEW

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

IT INCLUDES INFORMATION ON THE FOLLOWING:

- Patient alert card
- Indications
- Dosing recommendations and dose reduction
- Information on switching patients to and from LIXIANA®
- Contraindications
- Special patient populations
- Temporary discontinuation
- Overdose
- Perioperative management
- Cardioversion
- Management of bleeding complications
- Routine coagulation testing

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

# PATIENT ALERT CARD

## EVERY PATIENT PRESCRIBED LIXIANA® WILL RECEIVE A PATIENT ALERT CARD IN THE PACK WITH THEIR TABLETS.

This will inform doctors, dentists, pharmacists and other healthcare professionals about the patient's anticoagulation treatment, along with emergency contact details. Encourage patients to have this card with them at all times and to show it to healthcare professionals prior to any consultation or procedure.

Patients should be reminded of the importance of compliance to their treatment regime, the need to watch for signs and symptoms of bleeding and when to seek medical advice.

Patient Alert Cards are available from medinfo-ie@daiichisankyo.com or by calling 01 4893000.

# INDICATIONS

LIXIANA® (edoxaban) 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

# DOSING

## THE RECOMMENDED DOSE OF LIXIANA® IS **60 MG IN A ONCE-DAILY TABLET.**

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.

For patients who are unable to swallow whole tablets, Lixiana® tablets may be crushed and mixed with water or apple puree and immediately administered orally. Alternatively, Lixiana® tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water. Crushed Lixiana® tablets are stable in water and apple puree for up to 4 hours.

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 of 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

## DOSE REDUCTION

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

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

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

In order to prescribe the appropriate dose, it is important to measure creatinine clearance and body weight before the start of LIXIANA® therapy. Both results should be documented appropriately in the patient chart and should be checked and documented on a regular basis during ongoing treatment with LIXIANA®.

## INITIATING TREATMENT

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. The concomitant use of heparin (LMWH) and Lixiana® is contraindicated.

Renal function (CrCl) and liver function should be assessed in all patients prior to LIXIANA® initiation.

Information on switching patients to LIXIANA® from other treatments can be found on pages 6 to 9.

## MISSED DOSE

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.

## FROM NON-VKA ORAL ANTICOAGULANTS TO LIXIANA®

Discontinue the non-Vitamin K antagonist (VKA) oral anticoagulant and start LIXIANA® at the time of the next non-VKA dose.

## FROM LIXIANA® TO NON-VKA ORAL ANTICOAGULANTS

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

## FROM VKA THERAPY TO LIXIANA®

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

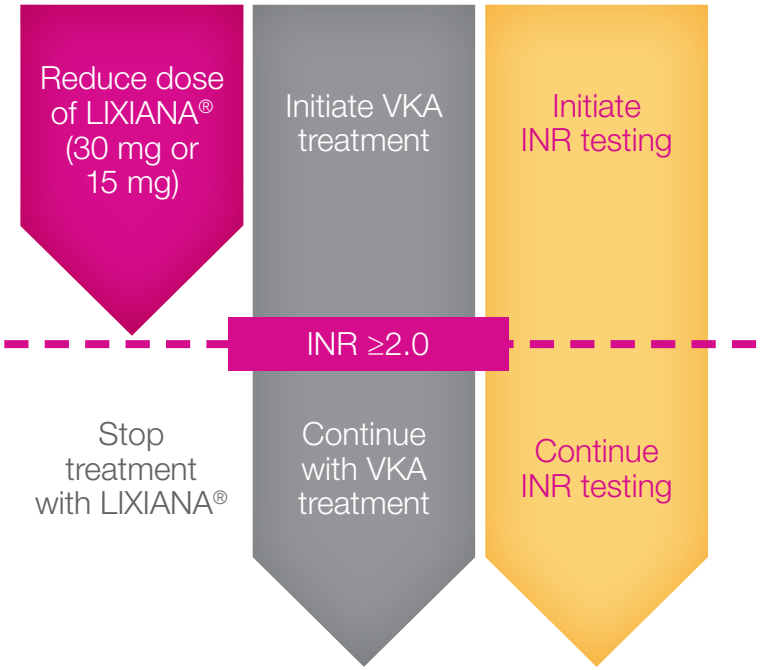
## FROM LIXIANA® TO VKA THERAPY

### ORAL OPTION

If switching a patient from LIXIANA® 60 mg to VKA therapy, administer a 30 mg dose of LIXIANA® once daily alongside appropriate VKA dose.

If switching a patient from LIXIANA® 30 mg to VKA therapy, administer a 15 mg dose of LIXIANA® once daily alongside appropriate VKA dose.

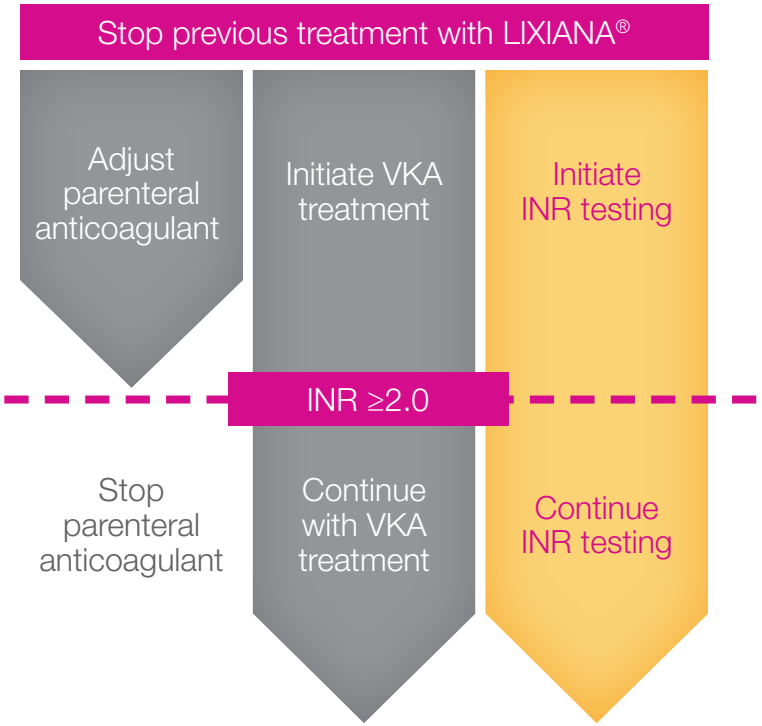
It is recommended that during the first 14 days of concomitant therapy, the INR is measured at least 3 times just prior to taking the daily dose of LIXIANA®. Continue to co-administer until stable INR ≥2.0 is achieved. At this point discontinue LIXIANA®. Most patients (85%) should be able to achieve an INR ≥2.0 within 14 days of concomitant therapy.




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.

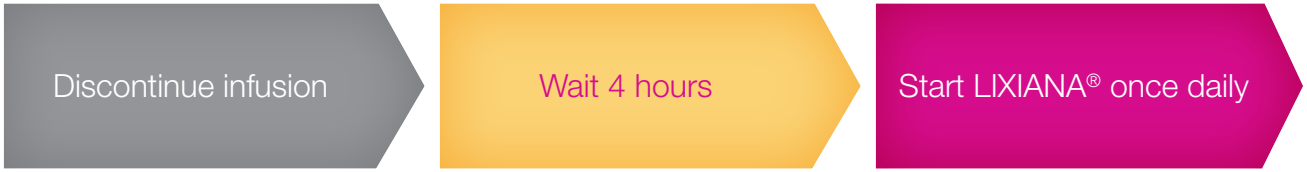
## PARENTERAL ROUTE

Discontinue LIXIANA® treatment, administer parenteral anticoagulant and VKA treatment at the time of the next scheduled LIXIANA® dose. When a stable INR of ≥2.0 is achieved, stop the parenteral anticoagulant and continue with VKA treatment.

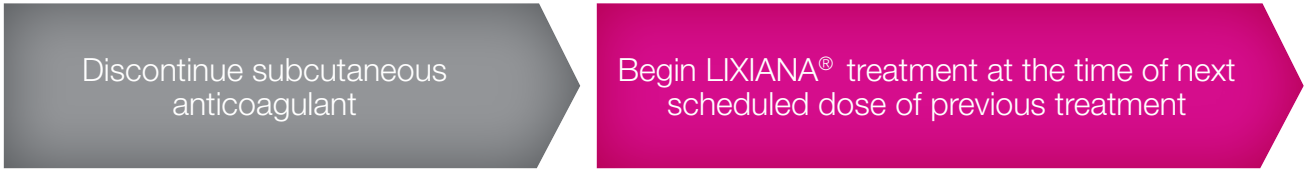


## FROM PARENTERAL ANTICOAGULANT TO LIXIANA®

LIXIANA® should not be administered simultaneously with a parenteral anticoagulant. Patients on continuously administered parenteral drug such as intravenous (IV) unfractioned heparin:




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




## FROM LIXIANA® TO PARENTERAL ANTICOAGULANT

LIXIANA® should not be administered simultaneously with parenteral anticoagulant. Discontinue LIXIANA® and administer the initial dose of 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.

| LIXIANA® is contraindicated in the following patients: |
|---|
| • 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:<br>– Current or recent gastrointestinal (GI) ulceration<br>– Malignant neoplasms at high risk of bleeding<br>– Recent brain or spinal injury or surgery<br>– Recent ophthalmic surgery<br>– Recent intracranial haemorrhage<br>– 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.

Prior to initiation of LIXIANA® and when clinically indicated, renal function testing (CrCl) should be performed and documented appropriately in the patient chart. Renal function should be routinely checked on a regular basis during ongoing treatment with Lixiana®.

| Patients with renal impairment | |
|---|---|
| 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 5) |
| Mild renal impairment (CrCl 51–80 mL/min) | No dose reduction required – 60 mg OD |

| Renal function in NVAF | |
|---|---|
| Patients with NVAF and high creatinine clearance | A trend towards decreasing efficacy with increasing CrCl was observed for LIXIANA® compared to well-managed warfarin. LIXIANA® should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk. Assessment of renal function: CrCl should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated. |

| Patients with hepatic impairment | |
|---|---|
| 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 | |
|---|---|
| P-gp inhibitors: ciclosporin, dronedarone, erythromycin, ketoconazole | Dose reduction to 30 mg OD (see Dose Reduction section on page 5) |
| Amiodarone, quinidine, verapamil or clarithromycin | No dose reduction required – 60 mg OD |
| P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitol or St John's 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

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.

# OVERDOSE

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.

# PERIOPERATIVE MANAGEMENT

In situations where a patient requires a surgical intervention or invasive procedure (including tooth extraction), LIXIANA® should be stopped 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. As LIXIANA® is a reversible Factor Xa inhibitor, its anticoagulant activity should lessen within 24–48 hours of the last administered dose.

If it is not possible to stop LIXIANA® at least 24 hours beforehand, or the procedure cannot be delayed, clinical judgement must be used to assess the bleeding risks in relation to the urgency of the intervention.

LIXIANA® should be restarted after the procedure 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®.

# CARDIOVERSION

LIXIANA® can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram (TOE) guided cardioversion in patients not previously treated with anticoagulants, LIXIANA® should be started at least 2 hours before cardioversion to ensure adequate anticoagulation.

Cardioversion should be performed no later than 12 hours after the dose of LIXIANA® as prescribed.

# MANAGEMENT OF BLEEDING COMPLICATIONS

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

In case of bleeding, measures should be individualised according to the severity and location of the haemorrhage:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the 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

Haemodialysis does not significantly contribute to LIXIANA® clearance.

# ROUTINE COAGULATION TESTING

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®.

Although treatment with LIXIANA® does not require routine monitoring, the effect on anticoagulation can be estimated by a calibrated quantitative anti-Factor Xa assay which may help to inform clinical decisions in particular situations as, e.g. overdose and emergency surgery.

Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It allows continued monitoring of the benefit / risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance: Website: www.hpra.ie
Adverse reactions should also be reported to Daiichi Sankyo Ireland Ltd. on (01) 4893000
or pharmacovigilance_ie@daiichisankyo.com

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Lixiana®
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