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Daiichi-Sankyo

Lixiana®
edoxaban

Prescriber Guide

LIXIANA® (edoxaban)

אישור משרד הבריאות לתאריך: אוגוסט 2021

THIS GUIDE IS SPECIFICALLY FOR PRESCRIBERS IN RELATION TO THE USE OF LIXIANA® (EDOXABAN). IT INCLUDES INFORMATION ON THE FOLLOWING:

- Important safety information
- Indications
- Contraindications
- Dosing recommendations and dose reduction
- Information on switching patients to or from Lixiana®
- Perioperative management
- Temporary discontinuation
- Drug-drug interactions
- Populations at higher risk of bleeding
- Overdose
- Bleeding complications
- Coagulation testing
- Patient alert card

Please consult the Physician Prescribing Information (PPI) for full prescribing information.

This medicinal product is subject to additional monitoring.

IMPORTANT SAFETY INFORMATION

For NVAF and VTE the recommended dose is 30 mg Lixiana® 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.

In patients with end stage renal disease or on dialysis, Lixiana® is not recommended.

Lixiana® should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.

Lixiana® administration should be discontinued if severe haemorrhage occurs.

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, Lixiana® should be stopped as soon as possible and preferably at least 24 hours before the procedure.
Should a bleeding complication arise in a patient receiving Lixiana®, the next Lixiana® administration should be delayed or treatment should be discontinued as appropriate.

The following sub-groups of patients are at increased risk of bleeding:
- Elderly
- Patients with renal impairment
- Patients with hepatic impairment

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.

CONTRAINDICATIONS

Lixiana® is contraindicated in the following patients:

- Those with hypersensitivity to the active substance.
- 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 breast feeding, it should be decided whether to cease therapy or to discontinue breast feeding.
- Those with uncontrolled severe hypertension.

DOSING

The recommended dose of Lixiana® is 60 mg in a once-daily tablet.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE): Initial use of parenteral anticoagulant for at least 5 days prior to the initiation of Lixiana® is required. Lixiana® and initial parenteral anticoagulant should not be administered simultaneously.

It can be taken with water, with or without food. To aid compliance, the 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

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] 15-50mL/min)**
- **Body weight ≤60 kg**
- **Concomitant use of the P-gp inhibitors dronedarone, cyclosporine, erythromycin, ketoconazole**

30 mg

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

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.

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.

PATIENTS UNDERGOING CARDIOVERSION

Lixiana® can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Lixiana® treatment 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® on the day of the procedure.
For all patients undergoing cardioversion: Confirmation should be sought prior to cardioversion that the patient has taken Lixiana® as prescribed. Decisions on initiation and duration of treatment should follow established guidelines for anticoagulant treatment in patients undergoing cardioversion.

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 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.

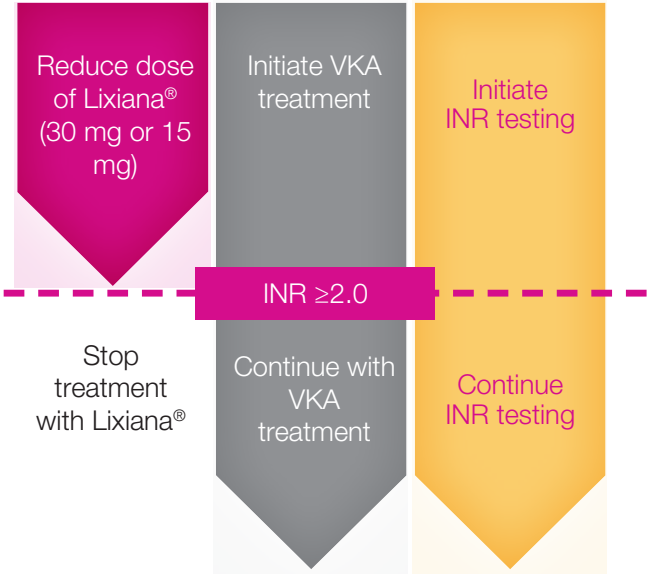
FROM LIXIANA® TO VKA THERAPY

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.

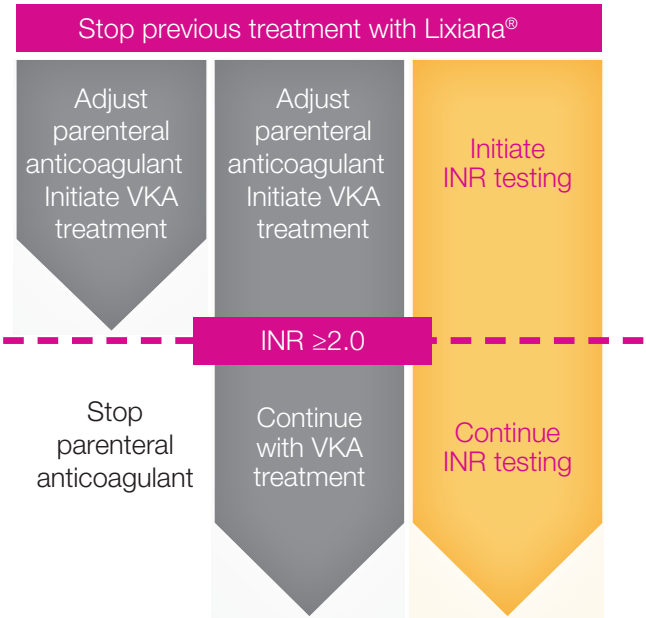
If switching a patient from Lixiana® 30 mg to VKA therapy, administer a 15 mg dose of Lixiana® once daily alongside appropriate VKA dose.

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®.



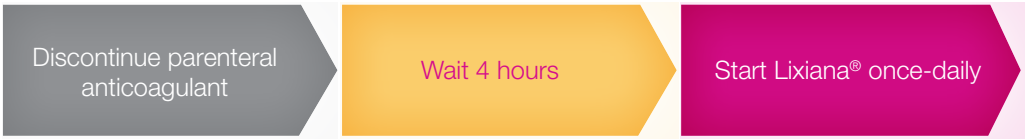
PARENTERAL ROUTE

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®

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



Patients on parenteral drug on fixed dose such as low molecular weight heparin (LMWH):

FROM LIXIANA® TO PARENTERAL ANTICOAGULANT

Administer the initial dose of parenteral anticoagulant at the time of the next schedule dose of Lixiana®.

Lixiana® should not be administered simultaneously with parenteral anticoagulant.

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 this is not possible to stop Lixiana® at least 24 hrs 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.

TEMPORARY DISCONTINUATION

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

DRUG-DRUG INTERACTIONS

Lixiana® is predominantly absorbed in the upper gastrointestinal (GI) tract. Thus, medicines or disease conditions that increase gastric emptying and gut motility have the possibility of reducing Lixiana® dissolution and absorption.
Concomitant use of medicines affecting haemostasis may increase the risk of bleeding.

P-gp inhibitors
Concomitant use of Lixiana® with ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily.
Concomitant use of Lixiana® with quinidine, verapamil, or amiodarone does not require dose reduction based on clinical data.
* Edoxaban decreased the Cmax and AUC of concomitantly administered verapamil.

P-gp inducers
The concomitant use of Lixiana® with other P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced Lixiana® plasma concentrations. Lixiana® should be used with caution when co-administered with P-gp inducers.

P-gp substrates
No dose modification is necessary when Lixiana® is administered with digoxin.

Anticoagulants
Co-administration of Lixiana® with other anticoagulants is contraindicated due to increased risk of bleeding.

ASA
The concomitant chronic use of high dose ASA (325 mg) with Lixiana® is not recommended.
Concomitant administration of higher doses than 100 mg ASA should only be performed under medical supervision. Lixiana® can be co-administered with low dose ASA (≤ 100 mg/day).

Platelet inhibitors
Concomitant use of thienopyridines (e.g. clopidogrel) monotherapy resulted in increased clinically relevant bleeding although with a lower risk of bleeding on Lixiana® compared to warfarin.
There is very limited experience on the use of Lixiana® with dual antiplatelet therapy or fibrinolytic agents.

NSAIDs
Co-administration of NSAIDs resulted in increased clinically relevant bleeding. Chronic use of NSAIDs with Lixiana® is not recommended.

SSRIs/SNRIs:
As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets.

PATIENTS AT POTENTIALLY HIGHER RISK OF BLEEDING

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

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.

Patients with renal impairment	
End stage renal disease: dialysis, renal failure (CrCL<15mL/min)	Not recommended
Moderate or severe renal impairment (CrCL 15–50mL/min)	Dose reduction to 30 mg OD (see Dose reduction section)
Mild renal impairment (CrCL 51–80mL/min)	No dose reduction required 60 mg OD

Prior to initiation of Lixiana® and when clinically indicated, renal function testing should be performed.

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

Patients receiving concomitant treatment	
P gp inhibitors: cyclosporine, dronedarone, erythromycin, ketoconazole	Dose reduction to 30 mg OD (see Dose reduction section)
Amiodarone, quinidine, or verapamil	No dose reduction required 60 mg OD
P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St Johns Wort)	Use with caution
P-gp substrates (digoxin)	No dose modification – 60 mg OD
Medication affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), or platelet aggregation inhibitors	Not recommended. Lixiana® can be coadministered with low dose ASA (≤ 100mg/day)
Chronic use of NSAIDs	Not recommended

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 edoxaban clinical programme.

MANAGEMENT OF BLEEDING COMPLICATIONS

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

In case of bleeding, initiation of measures stated below should be considered.

- 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 stated above, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50iU/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®.

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

PATIENT ALERT CARD

Please ensure that every patient prescribed Lixiana® receives a Patient Alert Card.

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 on www.health.gov.il or by calling 03-9250250.

REPORTING ADVERSE EVENTS

Adverse events can be reported to the Ministry of Health using the online form for adverse event reporting which can be found on the Ministry of Health website: www.health.gov.il or by using the following link: https://sideeffects.health.gov.il/

Adverse events can be also reported to Medison Pharma Ltd. according to following contact details:
Email: pv@medison.co.il, Fax: 03-9234218

This guide was revised and approved by the Ministry of Health in August 2021

Lixiana® edoxaban