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

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See page 14 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:

- Indications
- Dosing recommendations and dose reduction
- Information on switching patients to or from edoxaban
- Populations at higher risk of bleeding
- Perioperative management
- Temporary discontinuation
- Overdose
- Bleeding complications
- Coagulation testing

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

PATIENT ALERT CARD

A PATIENT ALERT CARD MUST BE PROVIDED TO EACH PATIENT WHO IS PRESCRIBED EDOXABAN

A patient alert card is included within each edoxaban tablet pack.

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 regimen, the need to watch for signs and symptoms of bleeding and when to seek medical advice.

Patient Alert Cards are available from medinfo@daiichi-sankyo.ie or by calling (01) 489 3000

INDICATIONS

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 EDOXABAN 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.

Treatment with edoxaban in patients with NVAF should be continued long term.

The duration of therapy for treatment of DVT and PE (venous thromboembolism, VTE) and prevention of recurrent VTE should be individualised after careful 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

For NVAF and VTE (DVT and PE) 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.

INITIATING TREATMENT

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

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

MISSED DOSE

If a patient misses a dose of edoxaban 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 EDOXABAN

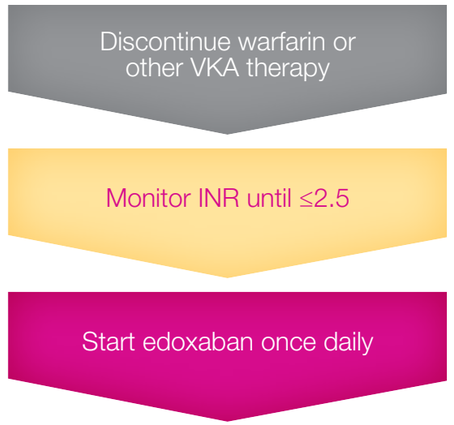
Switching patients to or from treatment with edoxaban is the same for both the VTE and NVAF indications. It should be noted that once a patient is switched to treatment with edoxaban, International Normalised Ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) are not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

FROM NON-VKA ORAL ANTICOAGULANTS TO EDOXABAN

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

FROM VKA THERAPY TO EDOXABAN

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



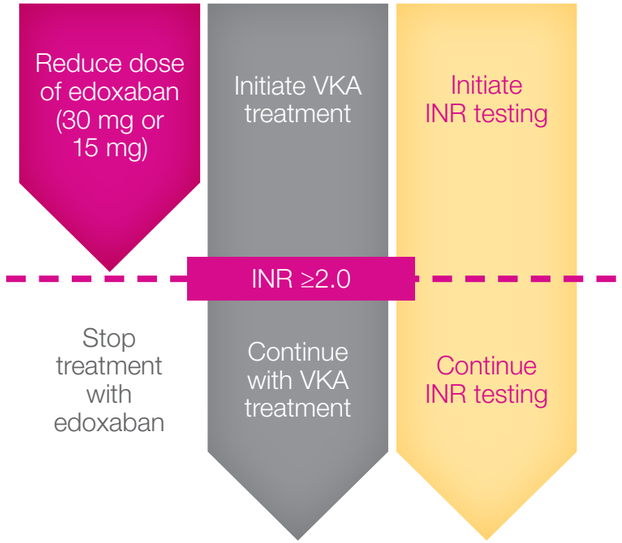
FROM EDOXABAN TO VKA THERAPY

ORAL OPTION

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

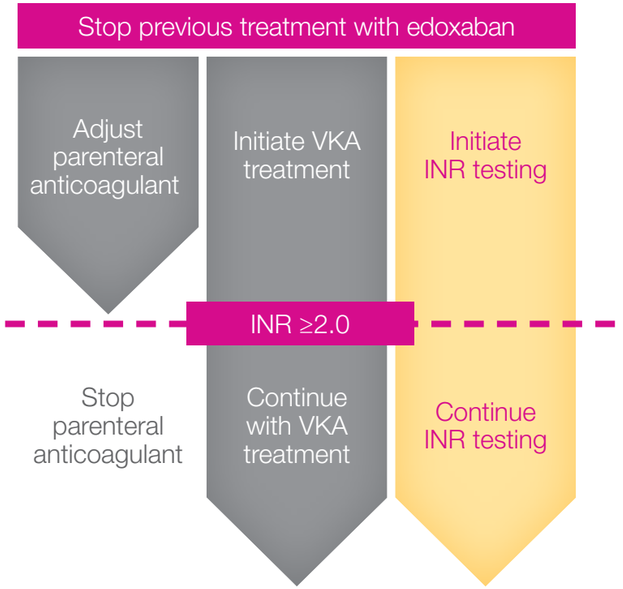
If switching a patient from edoxaban 30 mg to VKA therapy, administer a 15 mg dose of edoxaban once daily alongside appropriate VKA dose.

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 edoxaban. Continue to co-administer until stable INR ≥2.0 is achieved. At this point discontinue edoxaban.



PARENTERAL ROUTE

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



FROM PARENTERAL ANTICOAGULANT TO EDOXABAN

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

Discontinue parental anticoagulant → Wait 4 hours → Start edoxaban once daily

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

Begin edoxaban treatment at the time of next scheduled dose of previous treatment

FROM EDOXABAN TO PARENTERAL ANTICOAGULANT

Administer the initial dose of parenteral anticoagulant at the time of the next scheduled dose of edoxaban.

Edoxaban should not be administered simultaneously with parenteral anticoagulant.

PATIENTS AT POTENTIALLY HIGHER RISK OF BLEEDING

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

Edoxaban 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 edoxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
• Edoxaban is contraindicated during pregnancy and women of child-bearing potential should avoid becoming pregnant during treatment. As edoxaban is also contraindicated during breast feeding, it should be decided whether to cease therapy or to discontinue breast feeding
• 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.

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)
Mild renal impairment (CrCl 51–80 mL/min)	No dose reduction required – 60 mg OD

Prior to initiation of edoxaban 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

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

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, 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. edoxaban can be coadministered with low dose ASA (≤100 mg/day)
Chronic use of NSAIDs	Not recommended

PERIOPERATIVE MANAGEMENT

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

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 or tooth extraction), edoxaban should be restarted as soon as possible.

OVERDOSE

Overdose with edoxaban may lead to haemorrhage. A specific antidote antagonising the pharmacodynamic effect of edoxaban is not available. Early administration of activated charcoal may be considered in case of edoxaban 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 edoxaban 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 edoxaban (10–14hours) 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 50 iU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion

Haemodialysis does not significantly contribute to edoxaban clearance.

ROUTINE COAGULATION TESTING

Treatment with edoxaban does not require routine clinical coagulation monitoring.
As a result of Factor Xa inhibition, edoxaban 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 edoxaban.

There are no specific blood tests or assays available for edoxaban.

LIXIANA▼ (edoxaban) 60 mg/30 mg/15 mg film coated tablets

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information.

See summary of product characteristics prior to prescribing for full list of adverse events.

Presentation: 60 mg (yellow) / 30 mg (pink) / 15 mg (orange) edoxaban film coated tablets (as tosilate). **Indications:** 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) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology and method of administration:** *NVAF* - The recommended dose is 60 mg edoxaban once daily with or without food. Therapy with edoxaban in NVAF patients should be continued long term. *VTE* - The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days with or without food. Duration of therapy (at least 3 months) should be based on risk profile of the patient. 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 and/or concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. The 15 mg dose of edoxaban is not indicated as monotherapy, and should only be used during a switch from edoxaban to VKA (see SmPC for full details). If a dose of edoxaban is missed, the dose should be taken immediately and then continued once daily on the following day. **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 (GI) 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, low molecular weight heparins, heparin derivatives (fondaparinux, etc.), VKA or NOACs 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 breastfeeding. **Special warnings and precautions for use:** Haemorrhagic risk: Use with caution in patients with increased risk of bleeding such as elderly on ASA and 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. Haemodialysis does not significantly clear edoxaban. Renal impairment: Renal function should be assessed prior to initiation of edoxaban and afterwards when clinically indicated. Not recommended in patients with end stage renal disease or on dialysis. Renal function and NVAF: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful benefit risk evaluation. Hepatic impairment: Not recommended in patients with severe hepatic impairment and 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. *Surgery or other interventions:* discontinue edoxaban at least 24 hours before the procedure. If the procedure cannot be delayed, the increased risk of bleeding should be weighed against the urgency of the procedure. Edoxaban should be restarted as soon as haemostasis is achieved. *Prosthetic heart valves and moderate to severe mitral stenosis:* Not recommended. *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy:* Not recommended. *Patients with active cancer*: Not recommended. **Drug interactions:** The *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole result in increased concentration of edoxaban and a dose reduction of 30 mg is required. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. phenytoin, carbamazepine, phenobarbitol or St John's Wort). Concomitant high dose ASA (325 mg) or chronic NSAIDs is not recommended. There is very limited experience with dual antiplatelet therapy or fibrinolytic agents. **Pregnancy:** Not recommended. *Breastfeeding:* discontinue breastfeeding or edoxaban therapy. **Undesirable effects:** Common: anaemia, epistaxis, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gamma GT increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal. Uncommon: hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. Rare: anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Legal category:** POM. **Package quantities:** 60 mg/30 mg – 28 tablets. 15 mg – 10 tablets. **Marketing Authorisation (MA) number:** EU/1/15/993/001-16. **MA holder:** Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 Munich, Germany. **Additional Information:** Available on request from Daiichi Sankyo Ireland Ltd. Telephone: (01) 489 3000. Fax: (01) 489 3033. Email: medinfo@daiichi-sankyo.ie.

Date of preparation: July 2015.

▼This medicine is subject to additional monitoring.
Adverse events and product complaints should be reported.
To report an adverse event or a product complaint about a Daiichi Sankyo medicine, please call Daiichi Sankyo Ireland Ltd. on (01) 489 3000.
Healthcare professionals are also asked to report any suspected adverse reactions to Daiichi Sankyo medicines to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: (01) 676 4971; Fax: (01) 676 2517.
Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

References:

1. LIXIANA®, Summary of Product Characteristics, www.medicines.ie, September 2015.
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6. Buller HR *et al.* Poster presented at ESC 2013; Sept 1 2013, Amsterdam, Session 706.
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Date of item: August 2015
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