

LIXIANA (edoxaban) 60 mg / 30 mg / 15 mg film-coated tablets prescribing information

See Lixiana Summary of Product Characteristics (SmPC) prior to prescribing for full list of adverse events

Presentation: 60 mg (yellow) / 30 mg (pink) / 15mg (orange) edoxaban (as tosilate) film-coated tablets.

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 \geq 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.

Posology and method of administration: *NVAF:* Recommended dose is 60 mg edoxaban once daily with or without food. Continue therapy long term. *VTE:* Recommended dose is 60 mg edoxaban once daily with or without food following initial use of parenteral anticoagulant for at least 5 days. 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: moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min); low body weight \leq 60 kg; concomitant use of the 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 in certain patients (see SmPC for full details).

Edoxaban can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram guided cardioversion in patients not previously treated with anticoagulants, edoxaban 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 edoxaban on the day of the procedure. Confirm prior to cardioversion that the patient has taken edoxaban as prescribed.

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 including 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 DOACs 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: *Haemorrhagic risk:* Caution in patients with increased risk of bleeding such as elderly on ASA. Discontinue 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:* CrCl should be monitored at the 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 CrCl was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high CrCl after a careful benefit risk evaluation. *Hepatic impairment:* Not recommended in severe hepatic impairment. Caution in mild or moderate hepatic impairment. Caution in patients with elevated liver enzymes (ALT/AST $>$ 2 x ULN) or total bilirubin \geq 1.5 x ULN. Perform liver function testing prior to initiation and then periodically monitor for treatment beyond 1 year. *Surgery or other interventions:* discontinue edoxaban as soon as possible and preferably at least 24 hours before the procedure. If procedure cannot be delayed, the increased risk of bleeding should be weighed against urgency of the procedure. Restart edoxaban as soon as haemostasis 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 in treatment and/or prevention of VTE. *Patients with a history of thrombosis diagnosed with antiphospholipid syndrome:* DOACs including Edoxaban are not recommended.

Drug interactions: Concomitant use of the *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole requires edoxaban dose reduction to 30mg. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort). Concomitant high dose ASA (325 mg) or chronic NSAIDs is not recommended. Concomitant ASA at doses $>$ 100 mg and $<$ 325 mg should be under medical supervision only. Very limited experience with dual antiplatelet therapy or fibrinolytics. Possibility of increased bleeding risk with concomitant SSRIs or SNRIs.

Adverse reactions: *Common:* anaemia, dizziness, headache, epistaxis, abdominal pain, 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. *Serious uncommon:* thrombocytopenia, hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. *Serious 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:** 60mg / 30mg – 28 tablets.
15mg – 10 tablets. **Marketing Authorisation (MA) number:**
EU/1/15/993/018, EU/1/15/993/005, EU/1/15/993/001

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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) 4893000. 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) 6764971; Fax: (01)6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.