once-daily Lixiana® edoxaban

Determined Protection

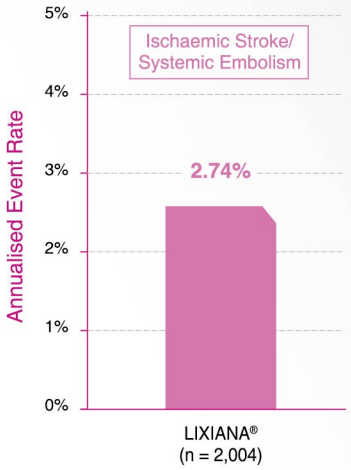
against Recurrent Stroke and Bleeding Events

LIXIANA® was **as efficacious as well-managed warfarin*** for stroke and systemic embolism prevention, **regardless** of a patient's **history of CVA/TIA**:[1]

Efficacy end point	LIXIANA® vs. warfarin	HR	95% CI	$p_{interaction}$
Stroke/SEE[1]				**0.86**
With previous stroke/TIA		0.86	(0.67 - 1.09)	
Without previous stroke/TIA		0.88	(0.72 - 1.08)	
All stroke[1]				**0.84**
With previous stroke/TIA		0.86	(0.67 - 1.10)	
Without previous stroke/TIA		0.89	(0.72 - 1.10)	
Fatal stroke[1]				**0.70**
With previous stroke/TIA		0.86	(0.53 - 1.40)	
Without previous stroke/TIA		0.97	(0.66 - 1.44)	

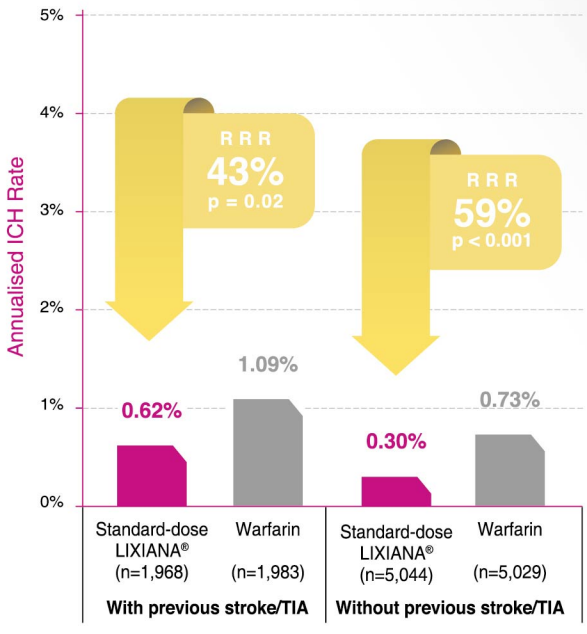
Low event rate with LIXIANA® in the real world among those **with cerebrovascular disease**:[2]

ETNA-AF-JAPAN



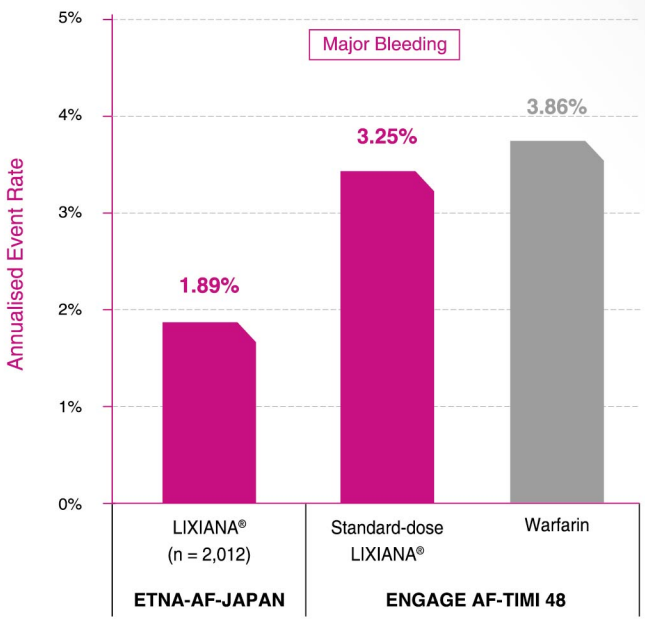
Significant risk **reduction in ICH** with LIXIANA® over warfarin extended to AF patients **with prior CVA/TIA** ($p_{interaction}$ = 0.28):[1]

ENGAGE AF-TIMI 48[1]



Incidences of **major bleeding** in patients **with cerebrovascular disease** were **low** in both phase III RCT and real-world data:[1,2]

Patients with cerebrovascular disease/events[1,2]



* Median time-in-therapeutic range: 68.4%.

AF = atrial fibrillation. CI = confidence interval. CVA = cerebrovascular accident. HR = hazard ratio. ICH = intracranial haemorrhage. RCT = randomised controlled trial. RRR = relative risk reduction. SEE = systemic embolic event. TIA = transient ischaemic attack.

Fewer Restrictions as Expected

Wider Range of Anticonvulsants Suited with the Use of LIXIANA® vs. Other DOACs[3,4]

LIXIANA® is **the only DOAC** which concomitant use of phenytoin or phenobarbital can be considered appropriate across different publications:*[3,4]

Established Antiepileptic Drugs (AEDs) | With Concurrent Use of LIXIANA®† (use with caution)[5]

- Carbamazepine‡,§,‖
- Phenytoin§,‖
- Phenobarbital§,‖

Being minimally involved in the metabolism through CYP3A4 (< 4%),[6] LIXIANA® can retain its anticoagulant effect in the presence of CYP3A4-inducing AEDs:

Newer AEDs | With Concurrent Use of LIXIANA®†

- Gabapentin[3]
- Lamotrigine¶,[3]
- Levetiracetam[4,7]
- Oxcarbazepine‖,[3,4]
- Pregabalin[3]
- Topiramate‖,¶,[3,4]

The materials for Lixiana® (Edoxaban) contained in this virtual exhibition are approved for use only in Hong Kong. Prescribing information may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and/or the Summary of Product Characteristics (SPC).

* Labelling (United States) of apixaban has recommended avoiding its concomitant use with P-gp and CYP3A4 (strong) dual inducers, e.g., phenytoin or phenobarbital.[6]
† As predicted.
‡ A case of significant interaction between carbamazepine and apixaban resulting in subtherapeutic drug concentrations and a TIA episode has been reported in the literature.[8] When the patient switched to LIXIANA® after the event, laboratory investigations indicated plasma levels of LIXIANA® were assured to therapeutic levels, despite the continued use of carbamazepine.[8]
§ P-gp inducer.[3] ‖ CYP3A4 inducer.[3] ¶ P-gp substrate.[3,9]

Study design: ENGAGE AF-TIMI 48 was a double-blind, double-dummy, randomised controlled trial[10] of patients (≥ 21 years old) with AF and a $CHADS_2$ score ≥ 2. Patients (n = 21,105) were randomised (1:1:1) to receive either high-dose LIXIANA® (60 mg), low-dose LIXIANA® (30 mg) or warfarin (dose-adjusted to INR of 2.0 - 3.0) for a median follow-up period of 2.8 years. Dose was halved in patients in both LIXIANA® arms if any of the following was present: 1) CrCl 30 - 50 mL/min, 2) body weight ≤ 60 kg, or 3) concomitant use of verapamil, quinidine or dronedarone. The primary efficacy end point was the time to the first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event.[10]

ETNA-AF-Japan is a real-world, prospective, open-label, observational study[2,11] of Japanese adult patients with NVAF, who were to receive LIXIANA® for the first time to prevent ischaemic stroke and systemic embolism. A total of 11,569 patients were enrolled, with a safety analysis set of 11,107 patients for the 1-year interim results.[2] The standard observation period was 2 years. Clinical outcomes (including AEs, e.g., bleeding events, and clinical events, e.g., death, stroke, systemic embolism, and MI) of included patients were collected on case report forms after 3, 12, and 24 months of study participation.[2,11]

AE = adverse event. AED = anti-epileptic drug. AF = atrial fibrillation. CrCl = creatinine clearance. CYP = cytochrome P450. DOAC = direct oral anticoagulant. INR = international normalised ratio. MI = myocardial infarction. NVAF = nonvalvular atrial fibrillation. P-gp = permeability glycoprotein. TIA = transient ischaemic attack.

References: 1. Rost NS, Giugliano RP, Ruff CT, et al.; ENGAGE AF-TIMI 48 Investigators. Stroke. 2016;47:2075-2082. **2.** Yamashita T, Koretsune Y, Nagao T, et al. J Arrhythm. 2020;36:395-405. **3.** Steffel J, Verhamme P, Potpara TS, et al.; ESC Scientific Document Group. Eur Heart J. 2018;39:1330-1393. **4.** Gelosa P, Castiglioni L, Tenconi M, et al. Pharmacol Res. 2018;135:60-79. **5.** LIXIANA® (edoxaban) package insert. Hong Kong; 2016 Sep. **6.** Wiggins BS, Dixon DL, Neyens RR, et al. J Am Coll Cardiol. 2020;75:1341-1350. **7.** Mathy FX, Dohin E, Bonfitto F, et al. Eur Heart J. 2019;40:1571. **8.** Di Gennaro L, Lancellotti S, De Cristofaro R, et al. J Thromb Thrombolysis. 2019;48:528-531. **9.** Stöllberger C, Finsterer J. Herz. 2015;40 Suppl 2:140-145. **10.** Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. N Engl J Med. 2013;369:2093-2104. **11.** Yamashita T, Koretsune Y, Ishikawa M, et al. J Arrhythm. 2019;35:121-129.

LIXIANA® 60 mg/30 mg/15 mg film-coated tablets.
Each film coated tablet contains 60 mg/30 mg/15 mg edoxaban (as tosilate). **List of excipients:** Mannitol (E421), Pregelatinised starch, Crospovidone, Hydroxypropylcellulose, Magnesium stearate (E470b), Hypromellose (E464), Macrogol 8000, Titanium dioxide (E171), Talc, Carnauba wax, Iron oxide yellow (E172), Iron oxide red (E172). **Therapeutic 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): 60 mg LIXIANA® once daily. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults: 60 mg LIXIANA® once daily following initial use of parenteral anticoagulant for at least 5 days. For NVAF and VTE 30 mg LIXIANA® once daily in patients with moderate or severe renal impairment (CrCl 15 - 50 mL/min), body weight ≤ 60 kg or concomitant use of P-glycoprotein (p-gp) inhibitors ciclosporin, dronedarone, erythromycin, or ketoconazole. **Contraindications:** Hypersensitivity to the active substance or 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. unfractionated heparin (UFH), low molecular weight heparins (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. **Undesirable effects:** Common: anaemia; epistaxis; lower GI haemorrhage; upper GI haemorrhage; oral/pharyngeal haemorrhage; nausea; blood bilirubin increased; gamma-glutamyl transferase 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); conjunctival/scleral haemorrhage; Intraocular haemorrhage; other haemorrhage; haemoptysis; blood alkaline phosphatase increased; transaminases increased; aspartate aminotransferase increased; urticaria; 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.
Please refer to Package Insert before prescribing. **Daiichi Sankyo Hong Kong Limited**

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