once-daily Lixiana® edoxaban

Expanding the Real-World Evidence Base

Confirming the Safety Profile of LIXIANA®

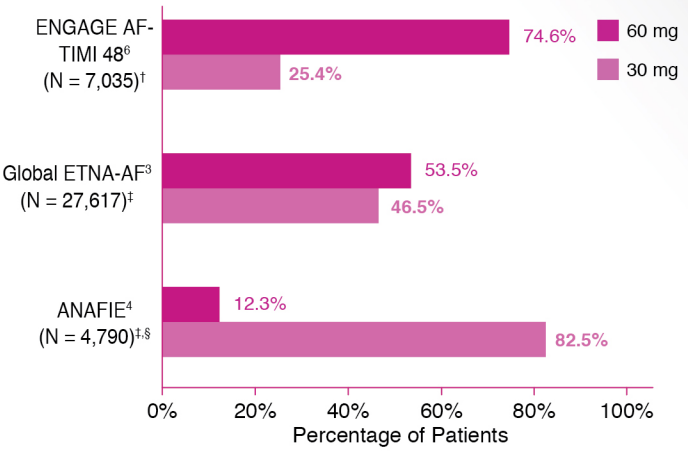
	Global ETNA-AF[1]	ANAFIE[2]
Countries Involved	Europe, Japan, and other Asian countries	Japan
No. of Patients Included[3,4]	27,617*	32,275*
Patient Characteristics	NVAF patients in routine clinical care	Elderly (≥ 75 years) NVAF patients in routine clinical setting
Anticoagulant Used	LIXIANA®	LIXIANA®, apixaban, rivaroxaban, dabigatran etexilate, warfarin, or not receiving OAC

* At 2-year follow-up.[3,4]

Both Global ETNA-AF and ANAFIE help accumulate the evidence supporting the effectiveness and safety of reduced-dose LIXIANA® (30 mg QD), especially in the elderly population:[4,5]

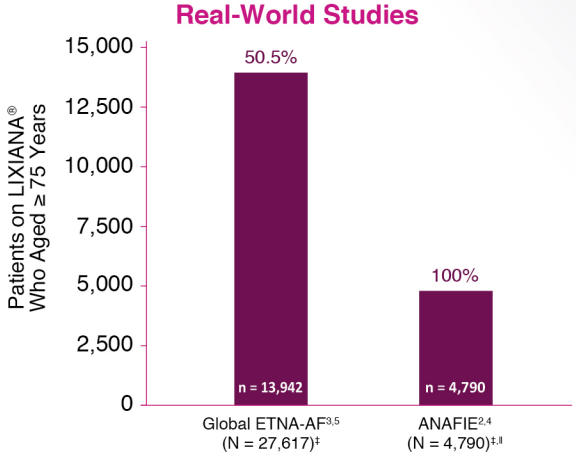
A total of over 18,500 patients from the randomised trial ENGAGE AF-TIMI 48, and the real-world studies Global ETNA-AF and ANAFIE were taking reduced-dose LIXIANA®:[3,4,6]

Dose Distribution across Different Studies



Global ETNA-AF and ANAFIE featured large numbers of patients who aged ≥ 75 years:[2,5]

Elderly (≥ 75 Years) Patients in Real-World Studies



† For those patients randomised to the standard-dose LIXIANA® arm. N = 21,105 for the overall ENGAGE AF-TIMI 48.[7]
‡ Number of patients at the 2-year follow-up.
§ For those patients taking LIXIANA® (not add up to 100% due to 5.2% of patients taking LIXIANA® at off-label doses of 15 mg or at other doses). N = 32,275 for the overall ANAFIE at the 2-year analysis.[4]
‖ For those patients taking LIXIANA®. The inclusion criteria of ANAFIE specified that patients had to be ≥ 75 years of age at the time of informed consent for enrolment.[2,4] N = 32,275 for the overall ANAFIE at the 2-year analysis.[4]

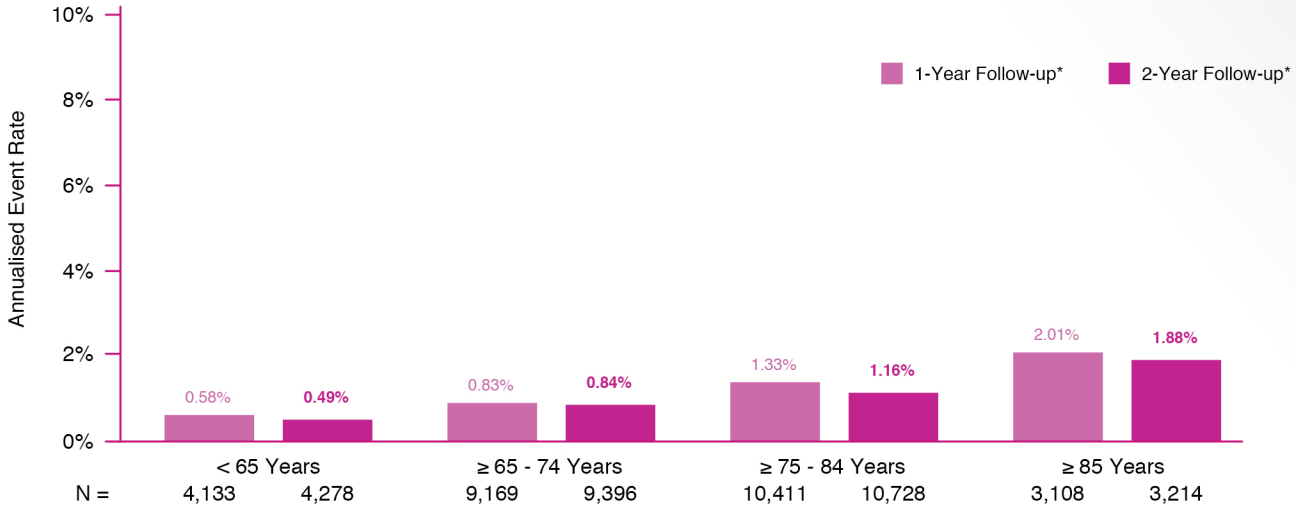
Low Rates of Major Bleeding in Routine Clinical Care

Evidence Built on Global ETNA-AF

Global ETNA-AF has demonstrated low rates of major bleeding with LIXIANA® in the elderly in routine clinical care:[5,8]

Major Bleeding Rates with LIXIANA® in the Real World[5,8]

Global ETNA-AF



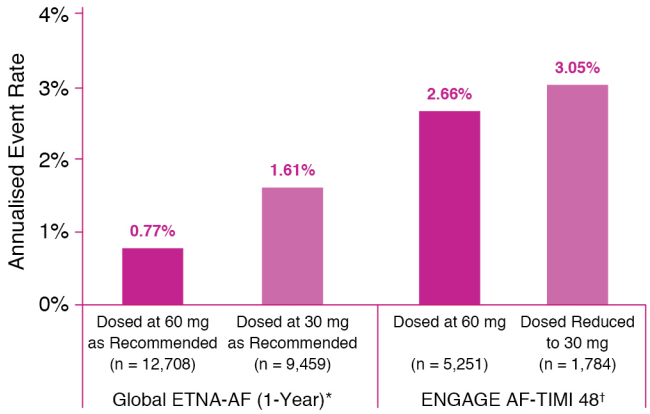
* N = 26,823 for the overall Global ETNA-AF at 1-year follow-up.[9] N = 27,617 for the overall Global ETNA-AF at 2-year follow-up.[3]

In the real world, with a minor age-dependent increase in bleeding risk, the observed major bleeding rates remained low across the age groups[5]

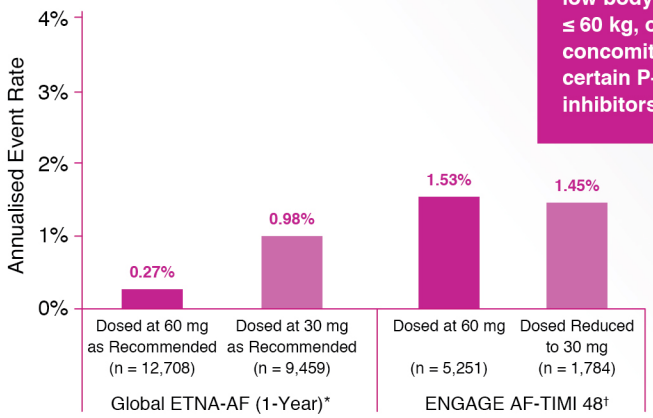
Global ETNA-AF provided an opportunity to demonstrate the safety of reduced-dose LIXIANA® in the real world:[10]

Bleeding Rates with Full-Dose and Reduced-Dose LIXIANA® in Real World and in RCT[6,10]

Major Bleeding (ISTH)



Major GI Bleeding



Patients being prescribed with or indicated for 30 mg would be those with moderate or severe renal impairment, low body weight ≤ 60 kg, or with concomitant use of certain P-gp inhibitors[11]

* N = 26,823 for the overall Global ETNA-AF at 1-year follow-up.[9] N = 27,617 for the overall Global ETNA-AF at 2-year follow-up.[3]
† N = 21,105 for the overall ENGAGE AF-TIMI 48.[7]

In the real world, patients on reduced-dose LIXIANA® were more likely to be at higher bleeding risk than those on full dose, yet major and GI bleeding rates were low among these patient groups[10]

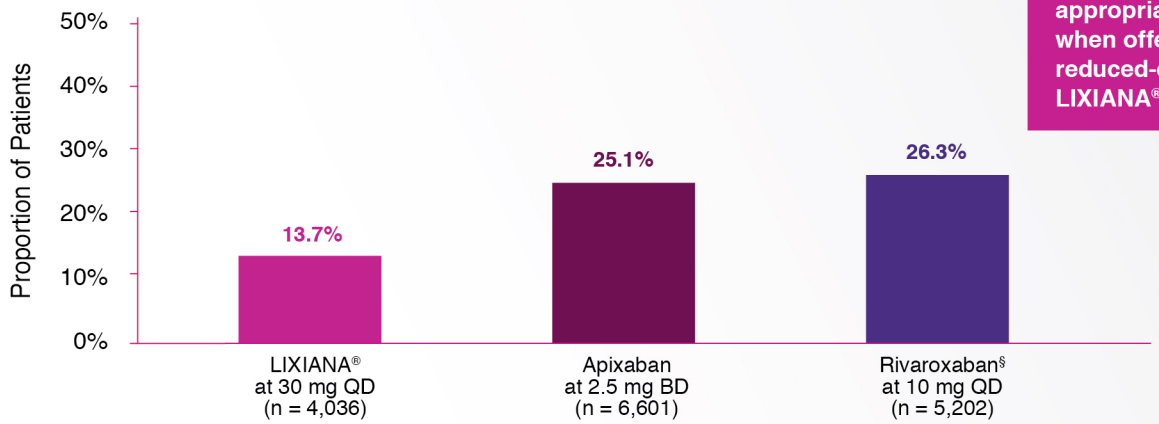
Think of Reduced-Dose DOACs, Think of LIXIANA®

Evidence Built on ANAFIE

Off-label under-dosing of LIXIANA® was presented in a low proportion of elderly NVAF patients, as per routine clinical practice in Japan:[12]

Patients on Off-Label Under-Dosing of DOACs‡,[12]

ANAFIE



Majority of patients would be appropriately dosed when offering reduced-dose LIXIANA®[12]

‡ Dose reduction "criteria" were not specified in dabigatran etexilate's label recommendations in Japan (but a "suggestion" for dose reductions for certain situations existed), therefore it cannot be defined if a patient taking reduced-dose dabigatran etexilate was underdosed inappropriately or not.

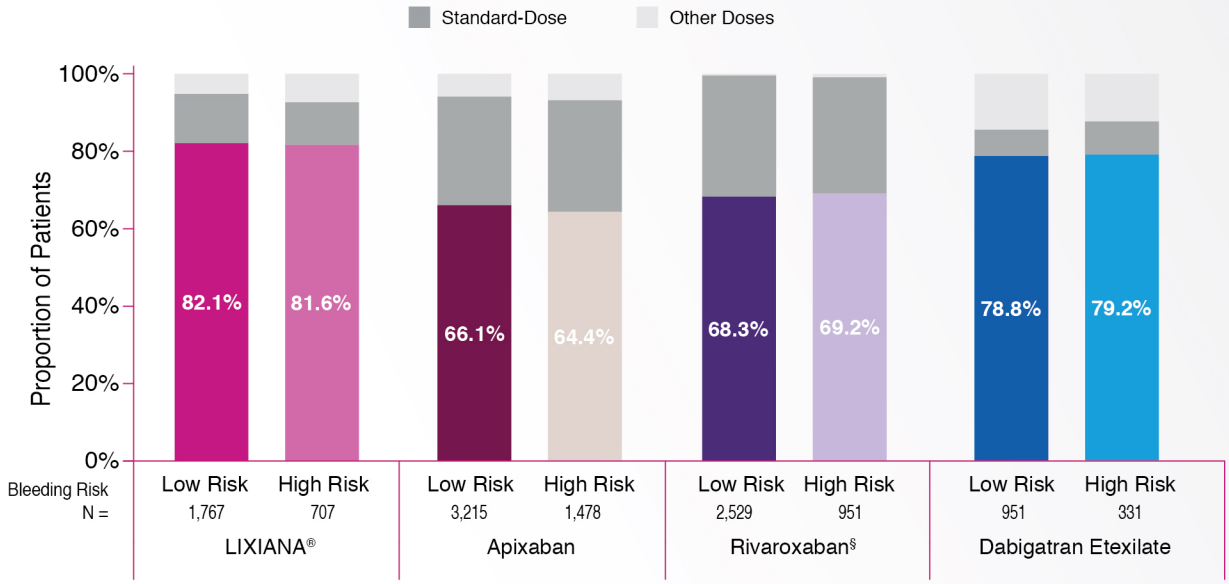
§ In the practice in Japan, standard-dose rivaroxaban and reduced-dose rivaroxaban refer to 15 mg QD and 10 mg QD respectively,[12] which differ from the practice in the locality (i.e., standard dose: 20 mg QD; reduced dose: 15 mg QD). Please refer to the local prescribing information of rivaroxaban for further information.

The simple dose reduction criteria of LIXIANA® allow patients who require a reduced-dose DOAC to be dosed appropriately[11,12]

Among these elderly patients at high risk of stroke who were taking LIXIANA®, over 80% of them were on LIXIANA® at reduced dose, regardless of baseline bleeding risk:[13]

Proportion of $CHADS_2 \geq 3$ Patients Receiving Reduced Doses with Different DOACs‖,[13]

ANAFIE

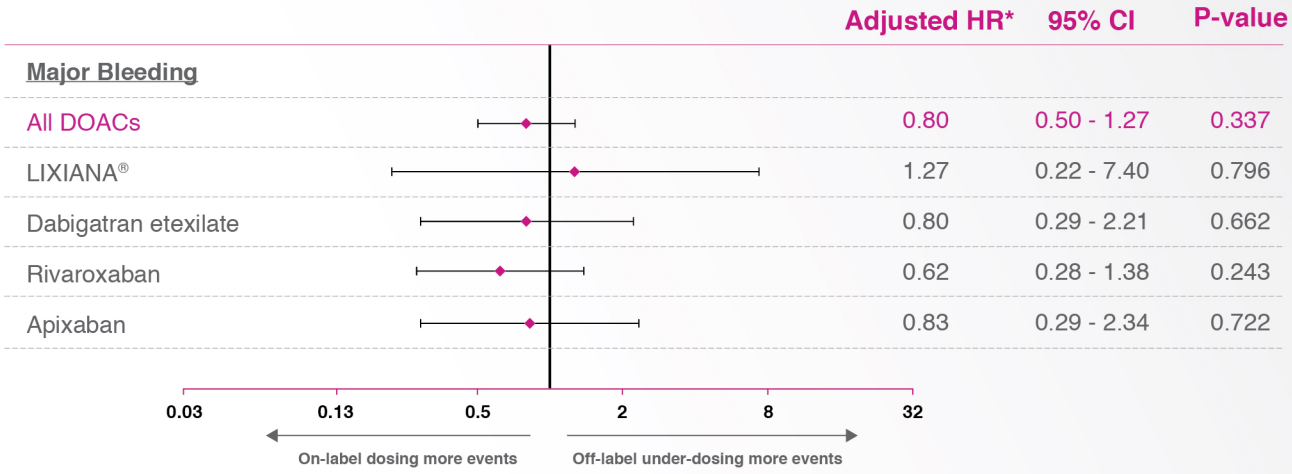


‖ Coloured portions of the bars. High bleeding risk referred to those with HAS-BLED ≥ 3, while low bleeding risk referred to those with HAS-BLED ≤ 2.
Reduced dose: 30 mg QD for LIXIANA®, 2.5 mg BD for apixaban, 10 mg QD for rivaroxaban§ and 110 mg BD for dabigatran etexilate. Standard dose: 60 mg QD for LIXIANA®, 5 mg BD for apixaban, 15 mg QD for rivaroxaban§ and 150 mg BD for dabigatran etexilate.

§ In the practice in Japan, standard-dose rivaroxaban and reduced-dose rivaroxaban refer to 15 mg QD and 10 mg QD respectively,[12] which differ from the practice in the locality (i.e., standard dose: 20 mg QD; reduced dose: 15 mg QD). Please refer to the local prescribing information of rivaroxaban for further information.

Off-Label Reduced-Dose DOACs Did Not Result in Less Bleeding

While physicians tend to prescribe reduced-dose DOACs for Asian AF patients, there were no significant reductions in major bleeding if the DOACs were inappropriately prescribed at reduced doses:[14]



* Adjusted for age, gender, CHA_2DS_2-VASc score, HAS-BLED score, and CrCl rate.

The Real-World Power of LIXIANA®

- Well-established usage of reduced dose in expanded numbers of patients[3,4]
- Simple dose reduction criteria to allow appropriate use of a reduced-dose DOAC[11,12]

Study design:
ENGAGE AF-TIMI 48 was a randomised, double-blind, double-dummy trial[7] 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.

Global ETNA-AF is an ongoing program[1] that integrates data from several prospective, observational, and non-interventional regional studies from Europe, Japan, and other Asian countries. Eligible patients were those treated with LIXIANA® for the first time to prevent ischaemic stroke and systemic embolism in AF, according to the local label. Follow-up time was 4 years for ETNA-AF EU and 2 years for ETNA-AF Japan and ETNA-AF East and Southeast Asia. In the 2-year follow-up analysis set, data from a total of 27,617 patients on LIXIANA® were included.[3] The primary goal was to evaluate the routine clinical usage, safety, and effectiveness of LIXIANA®.

ANAFIE was a prospective, multicentre, observational cohort study[2] as a real-world registry of elderly NVAF patients aged ≥ 75 years in Japan. Eligible patients were those who provided informed consent and were able to attend hospital visits, irrespective of OAC use (i.e., no treatment was mandated).[13] Follow-up data were collected at month 12 and month 24. In the 2-year outcome analysis, a total of 32,275 patients were included, with a mean follow-up of 1.88 years.[4] The primary outcome was a composite of stroke and systemic embolism.

In a retrospective observational study[14] conducted using patient data in Taiwan, chart records of 11,275 patients (≥ 20 years old) with new-onset NVAF and on an OAC were retrieved, and those on DOACs (LIXIANA®, apixaban, dabigatran etexilate, or rivaroxaban) were defined as "on-label dosing", "off-label under-dosing" or "off-label over-dosing", based on the dosage reduction criteria of pivotal DOAC randomised trials and recommendations of international society guidelines. Patients who were on "off-label under-dosing" or "off-label over-dosing" were compared with those on "on-label dosing", in terms of clinical outcomes of ischaemic stroke/systemic embolism and major bleeding. In total, 7,764 (68.9%) of patients were on on-label dosing compared with 2,999 (26.6%) on off-label under-dosing.

AF = atrial fibrillation. BD = twice daily. CI = confidence interval. CrCl = creatinine clearance. DOAC = direct oral anticoagulant. EU = European Union. FDA = United States Food and Drug Administration. GI = gastrointestinal. HR = hazard ratio. INR = international normalised ratio. ISTH = International Society on Thrombosis and Haemostasis. No. = number. NVAF = non-valvular atrial fibrillation. OAC = oral anticoagulant. QD = once daily. RCT = randomised controlled trial.

References: 1. De Caterina R, Agnelli G, Laeis P, et al. Clin Cardiol. 2019;42:1147-1154. **2.** Inoue H, Yamashita T, Akao M, et al. J Cardiol. 2018;72:300-306. **3.** Dinshaw L, Unverdorben M, Chen C, et al. Europace. 2021;23 Suppl 3:iii303-iii304. **4.** Yamashita T, Suzuki S, Inoue H, et al. Eur Heart J Qual Care Clin Outcomes. Epub 2021 Apr 2. doi: 10.1093/ehjqcco/qcab025. **5.** Morrone D, Unverdorben M, Chen C, et al. Europace. 2021;23 Suppl 3:iii301-iii302. **6.** Ruff CT, Giugliano RP, Braunwald E, et al. Lancet. 2015;385:2288-2295. **7.** Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. N Engl J Med. 2013;369:2093-2104. **8.** Yamashita T, Wang CC, Kim YH, et al. Eur Heart J. 2020;41 Suppl 2:663. **9.** De Caterina R, Kim YH, Koretsune Y, et al. J Clin Med. 2021;10:573. **10.** Chao TF, Kirchhof P, Koretsune Y, et al. Eur Heart J. 2020;41 Suppl 2:657. **11.** LIXIANA® (edoxaban) tablets 15 mg/30 mg/60 mg Hong Kong prescribing information. 2019 Jul. **12.** Akao M, Shimizu W, Atarashi H, et al. Circ Rep. 2020;2:552-559. **13.** Yasaka M, Yamashita T, Akao M, et al. BMJ Open. 2021;11:e044501. **14.** Chan YH, Chao TF, Chen SW, et al. Heart Rhythm. 2020;17:2102-2110.

Abbreviated Prescribing Information
LIXIANA® (edoxaban) 60 mg/30 mg/15 mg film-coated tablets. **Indications:** Prevention of stroke & systemic embolism in adult patients w/ nonvalvular atrial fibrillation (NVAF) w/ ≥ 1 risk factor e.g., CHF, HTN, ≥ 75 yr of age, DM, prior stroke or transient ischaemic attack. Treatment of DVT & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults. **Dosage:** Prevention of stroke & systemic embolism 60 mg once daily. Treatment of DVT & PE & prevention of recurrent DVT & PE (VTE) 60 mg once daily following initial use of parenteral anticoagulant for at least 5 days. Moderate or severe renal impairment (CrCl 15 - 50 mL/min), ≤ 60 kg body wt, concomitant use of the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole 30 mg once daily. **Contraindications:** Hypersensitivity. Clinically significant active bleeding; hepatic disease associated w/ coagulopathy & clinically relevant bleeding risk; lesion or condition, if considered to be a significant risk for major bleeding, including current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophth surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; uncontrolled severe HTN; concomitant treatment w/ any other anticoagulants e.g., unfractionated heparin (UFH), LMWH (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 & lactation. **Precaution:** LIXIANA 15 mg is not indicated as monotherapy. **Interactions:** Reduced dissolution & absorption w/ medicines or disease conditions that increase gastric emptying & gut motility. Increased plasma conc w/ P-gp inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole, quinidine, verapamil, amiodarone). Reduced plasma conc w/ P-gp inducers (rifampicin, phenytoin, carbamazepine, phenobarb or St. John's wort). Increased risk of bleeding w/ other anticoagulants; SSRIs or SNRIs. Increased bleeding time w/ ASA (≥ 100 mg). Increased clinically relevant bleeding w/ thienopyridines (e.g., clopidogrel); NSAIDs. **Undesirable effects:** Anaemia; dizziness, headache; epistaxis; abdominal pain, lower/upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea; increased blood bilirubin, increased γ-glutamyltransferase; cutaneous soft tissue haemorrhage, rash, pruritus; macroscopic haematuria/urethral haemorrhage. Version: Jul 2019. Please refer to the prescribing information before prescribing.

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