



# Summary of Investigation Results

## Apixaban Edoxaban tosilate hydrate Dabigatran etexilate methanesulfonate Rivaroxaban Warfarin potassium

November 21, 2023

### **Non-proprietary name**

Apixaban

Edoxaban tosilate hydrate

Dabigatran etexilate methanesulfonate

Rivaroxaban

Warfarin potassium

### **Brand name (marketing authorization holder)**

See appendix.

### **Japanese market launch**

See appendix.

### **Indications**

See appendix.

### **Summary of revisions**

“Acute kidney injury” should be added to the Clinically Significant Adverse Reactions section in ADVERSE REACTIONS.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

### **Investigation results and background of the revision**

Cases of acute kidney injury including anticoagulant-related nephropathy were evaluated. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS of oral anticoagulants was necessary based on the following reasons:

- Among oral anticoagulants, cases for which a causal relationship of warfarin potassium and multiple direct oral anticoagulants (edoxaban tosilate hydrate, dabigatran etexilate methanesulfonate, rivaroxaban) to acute kidney injury including anticoagulant-related nephropathy was reasonably possible have been reported.  
For apixaban, although no cases for which a causal relationship to acute kidney injury including anticoagulant-related nephropathy was reasonably possible have been reported in Japan, cases with a reasonably possible causal relationship to anticoagulant-related nephropathy have been reported in the literature published overseas (Kidney Res Clin Pract. 2017; 36: 387-392.).

While it was decided to use “acute kidney injury” instead of “anticoagulant-related nephropathy” for the name of the adverse reactions based on the following reasons, it was also decided to describe the findings characteristic to anticoagulant-related nephropathy (haematuria, numerous red cell casts in the renal tubules, etc.) reported in the published literature and case reports of adverse drug reactions.

- Anticoagulant-related nephropathy is considered to be a form of acute kidney injury (J Am Soc Nephrol. 2018; 29: 2787-2793., Adv Clin Exp Med. 2022; 31: 165-173.).
- No guidelines, etc. on anticoagulant-related nephropathy by related academic societies are available, and the disease is not considered to be generally well recognized.

### **Reference: Number of cases\* and patient mortalities involving acute kidney injury (including anticoagulant-related nephropathy) reported in Japan**

- a. A total of 7 cases have been reported to date. (A causal relationship between the drug and event could not be established for these cases.)

A total of 3 patient mortalities have been reported to date. (A causal relationship

between the drug and death subsequent to the event could not be established for these cases.)

- b. A total of 6 cases have been reported to date (including 4 cases for which a causal relationship between the drug and event was reasonably possible).

One instance of patient mortality has been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for this case.)

- c. A total of 26 cases have been reported to date (including 7 cases for which a causal relationship between the drug and event was reasonably possible).

A total of 3 patient mortalities have been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for these cases.)

- d. A total of 6 cases have been reported to date (including 3 cases for which a causal relationship between the drug and event was reasonably possible).

One instance of patient mortality has been reported to date. (A causal relationship between the drug and death subsequent to the event could not be established for this case.)

- e. A total of 7 cases have been reported to date (including 4 cases for which a causal relationship between the drug and event was reasonably possible).

No patient mortalities have been reported to date.

\*: Among the cases retrieved for adverse reactions (PT) of “anticoagulant-related nephropathy” or “acute kidney injury” from the PMDA's database for adverse drug reactions, etc. reports, those falling under both of the conditions described below were subjected to evaluation.

- 1) Information on renal function values (serum creatinine levels, etc. at baseline and onset) required for the diagnosis of acute kidney injury in Clinical Practice Guideline for Acute Kidney Injury 2016 (the committee for preparation of Clinical Practice Guideline for Acute Kidney Injury, edited by Japanese Society of Nephrology, the Japanese Society of Intensive Care Medicine, the Japanese Society for Dialysis Therapy, Japan Society for Blood Purification in Critical Care,



*This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

the Japanese Society for Pediatric Nephrology) is available, and it satisfies the diagnostic criteria for acute kidney injury.

- 2) Information on outcomes after the onset of adverse reactions (including information in the column of clinical course and laboratory tests) necessary for the assessment of a causal relationship is available.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).



This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Attachment

List of oral anticoagulants

	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
a.	Apixaban	Eliquis tablets 2.5 mg, 5 mg	Bristol-Myers Squibb K.K.	February 2013	<ul style="list-style-type: none"> <li>•Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation</li> <li>•Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism)</li> </ul>
b.	Edoxaban tosilate hydrate	Lixiana Tablets 15 mg, 30 mg, 60 mg, Lixiana OD Tablets 15 mg, 30 mg, 60 mg	Daiichi Sankyo Co., Ltd.	<Tablets> July 2011 <OD Tablets> November 2017	<ul style="list-style-type: none"> <li>•Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation</li> <li>•Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism)</li> <li>•Prevention of venous thromboembolism in patients undergoing any of the following orthopedic surgeries for the lower limbs &lt;excluding 60 mg&gt;                      Total knee replacement, total hip replacement, and hip fracture surgery</li> </ul>
c.	Dabigatran etexilate methanesulfonate	Prazaxa Capsules 75 mg, 110 mg	Boehringer Ingelheim Japan, Inc.	March 2011	Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
d.	Rivaroxaban	Xarelto tablets 2.5 mg, 10 mg, 15 mg, Xarelto OD tablets 10 mg, 15 mg, Xarelto fine granules 10 mg, 15 mg, Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg	Bayer Yakuin Ltd.	<tablets 2.5 mg> October 2022 <tablets 10 mg, 15 mg> April 2012 <OD tablets 10 mg, 15 mg> <granules> January 2021 <fine granules> December 2015 <dry syrup for pediatric> July 2021	<tablets 2.5 mg> Prevention of thrombus/embolization formation in patients with peripheral arterial disease after lower limb revascularization surgery <tablets 10 mg, 15 mg, OD tablets 10 mg, 15 mg, fine granules> Adults <ul style="list-style-type: none"> <li>•Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation</li> <li>•Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism)</li> </ul> Children

*This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

					<ul style="list-style-type: none"> <li>•Treatment and prevention of the relapse of venous thromboembolism.</li> </ul> <dry syrup> Treatment and prevention of the relapse of venous thromboembolism
e.	Warfarin potassium	Warfarin tablets 0.5 mg, 1 mg, 5 mg, Warfarin granules 0.2%, and the others	Eisai Co., Ltd., and the others	<tablets 0.5 mg> May 2004 <tablets 1 mg> May 1962 <tablets 5 mg> December 1976 <granules 0.2%> December 2011	Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, slowly progressive cerebral thrombosis, etc.)