独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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.

Summary of Investigation Results

Apixaban
Edoxaban tosilate hydrate
Dabigatran etexilate methanesulfonate
Rivaroxaban
Warfarin potassium

November 26, 2025

Non-proprietary name

Apixaban

Edoxaban tosilate hydrate

Dabigatran etexilate methanesulfonate

Rivaroxaban

Warfarin potassium

Brand name (marketing authorization holder)

See Attachment

Japanese market launch

See Attachment

Indications

See Attachment

Summary of revisions

"Splenic haemorrhage leading to splenic rupture" should be added to the "Haemorrhage" section in the 11.1 Clinically Significant Adverse Reactions section in the 11. ADVERSE REACTIONS section.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
Contact: https://www.pmda.go.jp/english/contact/0001.html

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.

Investigation results and background of the revision

Cases reported in Japan and overseas and the results of a disproportionality analysis using the WHO Individual Case Safety Reports (ICSRs) Global Database (VigiBase)[*1] were evaluated for the risk of splenic rupture associated with oral anticoagulants. 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 was necessary, taking into consideration the following:

- Cases of adverse reactions and literature reports in which the causal relationship between splenic rupture and oral anticoagulants was reasonably possible have been reported for multiple oral anticoagulants (apixaban, dabigatran, rivaroxaban, warfarin) in Japan and overseas*[2].
- Although the mechanism of splenic rupture caused by oral anticoagulants has not been clarified, in the literature, it is presumed that changes in the hemostatic mechanism within the spleen lead to splenic hemorrhage and result in splenic rupture during treatment with oral anticoagulants*3,4,5. Considering the presumed mechanism, splenic rupture can be a potential risk for the drug class of oral anticoagulants.
- The disproportionality analysis using VigiBase showed statistically higher numbers of reported adverse reactions involving “splenic rupture” for all the five ingredients of oral anticoagulants than would be expected based on the entire database[*6] (see Attachment).

Reference: Number of cases and patient mortalities involving splenic rupture in Japan[*7] and overseas[*8]

[1] One case has been reported in Japan to date (A causal relationship between the drug and the event could not be established for this case).
No patient mortalities have been reported.
[5] A total of 5 cases have been reported in Japan to date (including 4 cases in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported.
[2], [3], [4] No cases have been reported in Japan to date.

[3] A total of 9 cases have been reported overseas to date (including 4 cases in which a causal relationship between the drug and the event was reasonably possible).

A total of 2 patient mortalities have been reported overseas to date (no cases in which a causal relationship between the drug and the death following the event was reasonably possible).
[4] A total of 4 cases have been reported overseas to date (including 2 cases in which a causal relationship between the drug and the event was reasonably possible).
No patient mortalities have been reported.
[1], [2], [5] No cases have been reported overseas to date.

*1: Data from VigiBase, the WHO global database of reported adverse events of medicinal products, were used for this analysis Causal relationships between the event and a medicine may be difficult to establish due to limitations in the data.
*2: Lowry LE, et al. :J Med Case Rep. 2016;10(1):217
*3: Birte S. Steiniger et al. :Sci. Rep. 2022;12:16487
*4: Kaufman N, et al. :BMJ Case Rep. 2017;doi:10.1136/bcr-2017-221288
*5: Jessica B, et al :JCHIMP. 2022;12(5):84-87
*6: The information, results, and conclusions drawn do not represent the opinions of the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, or of the World Health Organization.
*7: Among the cases retrieved for adverse reactions (PT) of “Splenic rupture”, “Spontaneous splenic rupture”, “Splenic haemorrhage”, “Splenic haematoma”, “Subcapsular splenic haematoma”, and “Splenic injury” from those collected in the PMDA's safety database for adverse drug reactions, etc. reports, cases meeting any of the following conditions 1) to 4) were excluded.

1) No splenic rupture occurs.
2) Patients have diseases, etc. considered to be causally related to splenic rupture (including splenic angiosarcoma, pancreatic carcinoma, gastrointestinal carcinoma with splenic metastasis, hematopoietic tumor with splenomegaly/portal hypertension)
3) Splenic rupture is considered to have been caused by trauma.
4) The pathological examination required for evaluation of the causal relationship has not been performed or whether the examination has been performed or not is unknown.

*8: In the PMDA's safety database for adverse drug reactions, etc. reports and among the cases presented in the references (case reports) for the safety review conducted by Health Canada or those presented by the marketing authorization holders as the cases in which the

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.

relationship between a drug and an event (splenic rupture) is suspected, the cases meeting any of the conditions 1) to 4) provided in *7 were excluded.

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	Date of Initial Marketing in Japan	Indications
[1]	Apixaban	Eliquis tablets 2.5 mg, Eliquis tablets 5 mg	Bristol-Myers Squibb K.K.	February 2013	○ Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation ○ Treatment and prevention of the recurrence of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism)
[2]	Edoxaban tosilate hydrate	Lixiana tablets 15 mg, Lixiana tablets 30 mg, Lixiana tablets 60 mg, Lixiana OD Tablets 15 mg, Lixiana OD tablets 30 mg, Lixiana OD tablets 60 mg	Daiichi Sankyo Co., Ltd.	< Tablets > July 2011 <OD tablets > November 2017	< Tablets 15 mg, tablets 30 mg, OD tablets 15 mg, OD tablets 30 mg> ○ Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation ○ Treatment and prevention of the recurrence of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) ○ Prevention of thrombus/embolus formation in patients with chronic thromboembolic pulmonary hypertension ○ Prevention of venous thromboembolism in patients undergoing orthopedic surgery of lower limbs including followings Total knee arthroplasty, total hip arthroplasty, and hip fracture surgery < Tablets 60 mg, OD tablets 60 mg >

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.

	Non-proprietary name	Brand name	Marketing authorization holder	Date of Initial Marketing in Japan	Indications
					○ Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation ○ Treatment and prevention of the recurrence of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) ○ Prevention of thrombus/embolus formation in patients with chronic thromboembolic pulmonary hypertension
[3]	Dabigatran etexilate methanesulfonate	Prazaxa Capsules 75 mg, Prazaxa Capsules 110 mg	Nippon Boehringer Ingelheim Co ., Ltd.	March 2011	Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation
[4]	Rivaroxaban	Xarelto tablets 2.5 mg, Xarelto tablets 10 mg, Xarelto tablets 15 mg, Xarelto OD tablets 10 mg, Xarelto OD tablets 15 mg, Xarelto fine granules 10 mg, Xarelto fine granules 15 mg, Xarelto dry syrup for pediatric 51.7 mg, Xarelto dry syrup for	Bayer Yakuhin, Ltd., etc.	< Tablets 2.5 mg > October 2022 < Tablets 10mg, 15 mg > April 2012 < OD tablets 10mg, OD tablets 15 mg > January 2021 < Fine granules 10 mg, 15 mg > December 2015	< Tablets 2.5 mg > Adults ○Inhibition of thrombus/embolization formation in patients with peripheral arterial disease after lower extremity revascularization Children ○Inhibition of thrombus/embolization formation in patients after Fontan surgery < Tablets 10 mg, tablets 15 mg, OD tablets 10 mg, OD tablets 15 mg, fine granules 10 mg, fine granules 15 mg > Adults

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
Contact: https://www.pmda.go.jp/english/contact/0001.html

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.

	Non-proprietary name	Brand name	Marketing authorization holder	Date of Initial Marketing in Japan	Indications
		pediatric 103.4 mg, etc.		< Dry syrup for pediatric 51.7 mg, 103.4 mg > July 2021	○ Prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation ○ Treatment and prevention of the recurrence of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) Children ○ Treatment and prevention of recurrent venous thromboembolism ○Inhibition of thrombus/embolization formation in patients after Fontan surgery < Dry syrup for pediatric 51.7 mg, 103.4 mg > ○ Treatment and prevention of recurrent venous thromboembolism ○Inhibition of thrombus/embolization formation in patients after Fontan surgery
[5]	Warfarin potassium	Warfarin tablets 0.5 mg, Warfarin tablets 1 mg, Warfarin tablets 5 mg, Warfarin granules 0.2%, etc.	Eisai Co., Ltd., etc.	< Tablets 0.5 mg > May 2004 < Tablets 1 mg> May 1962 < Tablets 5 mg> December 1976 < Granules 0.2%> December 2011	Treatment and prophylaxis of thromboembolism (e.g., phlebothrombosis, myocardial infarction, pulmonary embolism, brain embolism, slowly progressive cerebral thrombosis)