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Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

TO REPORT AN ADVERSE DRUG REACTION

Scan, Fill, Submit

Online

1. Visit www.bpfk.gov.my.
2. Click on ADR Reporting and Product Complaints.
3. Click to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Mail

1. Print out the ADR form available on website and complete it.
2. Mail or fax to:
   The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Telephone

03-7883 5400
(ext. 5542/ 8461/ 8463)

Fax

03-7956 7151

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- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)

Comparison and Updates on New Oral Anticoagulants (NOACs)

New oral anticoagulants (NOACs) comprise of dabigatran etexilate (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®). They have been developed as an alternative to warfarin (a Vitamin K antagonist) and offer some benefits over warfarin such as do not require blood monitoring as well as dietary restriction. NOACs are indicated for prevention of stroke and embolism in patients with non-valvular atrial fibrillation (NVAF). With the increasing use of these relatively new drugs, post-marketing monitoring is important to ensure safety. Pradaxa®, Xarelto® and Eliquis® were registered in Malaysia since 2009, 2010 and 2013 respectively.

Comparison of the three NOACs:

Product Name (Active ingredient)	**Pradaxa® (Dabigatran Etexilate)**	**Xarelto® (Rivaroxaban)**	**Eliquis® (Apixaban)**
Malaysian Drug Control Authority (DCA) approved Indications*	*75mg & 110mg capsule*: Primary prevention of venous thromboembolic events (VTE) in adults with hip or knee replacement surgery *110mg & 150mg capsule:* Reduction of the risk of stroke and systemic embolism in patients with NVAF.	*10mg*: Prevention of VTE in adults with hip or knee replacement surgery. *15mg & 20mg*: Prevention of stroke and systemic embolism in adults with NVAF. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.	*2.5mg*: Prevention of VTE in adults with hip or knee replacement surgery. *2.5mg & 5mg*: Prevention of stroke and systemic embolism in adults with NVAF.
Ministry of Health Malaysia Drug Formulary (*FUKKM*)-approved prescriber category and indications	• Prescriber category: A* • Same as DCA approved indication	• Prescriber category: A* • Same as DCA approved indication	• Not in FUKKM
Contraindications*	• Hypersensitivity to the active substance or excipients. • Clinically significant active bleeding. • Hepatic disease which is associated with coagulopathy.		
	• Severe renal impairment (CrCl<30ml/min). • Organic lesion at risk of bleeding. • Haemostasis impairment. • Concomitant treatment with quinidine or ketoconazole. • Prosthetic heart valve.	• Pregnancy. • Breastfeeding.	• Lesion or condition at significant risk of major bleeding. • Concomitant treatment with any other anticoagulant agent.
Renal excretion	80%	33%	25%
Use in renal impairment*			
CrCl <15ml/min	Contraindicated	Not recommended	Not recommended
CrCl 15-29ml/min		• Caution, as rivaroxaban plasma concentrations increased • Refer to package inserts (PI) for dose adjustments based on indication	• Caution, as apixaban plasma concentrations increased • Refer to PI for indication-specific dose adjustments
CrCl 30-49ml/min	• Refer to PI for indication-specific dose adjustments • Assess renal function at least once a year		No dosage adjustment
CrCl ≥50ml/min	No dosage adjustment required		
Use in dialysis	Limited clinical experience (50-60% dialysable)	Limited clinical data (Not expected to be dialysable)	Not recommended

Please refer to the approved package inserts (PI) for full details

In Malaysia, **bleeding-related events** are the most reported adverse reaction for NOACs. Statistics from the NPCB Drug Safety Monitoring Centre showed that out of the total ADR reports received for each product, 37 events (33.9%) for Pradaxa® and 16 events (59.3%) for Xarelto® were related to bleeding. As Eliquis® is newly registered in Malaysia, NPCB has only received one report for this product, which was on gastrointestinal and rectal bleeding.

There were four reports related to **stroke**, with two each involving Pradaxa® and Xarelto®. Out of the four reports, two were given causality C3 (probable) and the other two were assigned causality C4 (unlikely). Concomitant drugs and concurrent diseases were reported in three cases and no information was provided for the remaining report. One of the reports involved a fatal outcome (post-operative ischemic stroke), however this case was assigned a causality C4 (unlikely) because the NOAC was stopped one day before the emergency spinal operation and not continued post-operation. The patient also had concurrent disease and concomitant medications.

Advice for Healthcare Professionals :

- Close clinical surveillance (for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if multiple risk factors are present.
- Renal function should be assessed in all patients before starting dabigatran (Pradaxa®) and at least once a year in patients older than 75 years or those with a suspected decline in renal function.
- The Drug Safety Monitoring Centre, NPCB is conducting further review on the safety of these products. Detailed safety advice, including changes to the package inserts, will be published once this review has been completed.
- Any adverse events suspected to be associated with the use of NOACs should be reported to the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.