



Safety Notice 014/11

Newer Oral Anticoagulants

9 November 2011

Distributed to:

- Chief Executives
- Directors of Clinical Governance

Action required by:

- Directors of Clinical Governance

We recommend you also inform:

- ED Clinicians
- Medical and Surgical Department Heads
- Directors of Pharmacy
- Drug and Therapeutic Committees.

Expert Reference Group

Information provided by:

- Clinical Excellence Commission
- NSW TAG
- Therapeutics Goods Administration
- WSLHD Drug & Therapeutic Committee

Clinical Safety Quality and Governance Branch

NSW Ministry of Health

Tel. 02 9391 9200

Fax. 02 9391 9556

Email quality@doh.health.nsw.gov.au

<http://internal.health.nsw.gov.au/quality/sabs/>

The following newer oral anticoagulants are available in Australia. Patients may be initiated on these agents in hospital or in the community for a number of indications (refer page 2)

Rivaroxaban (Xarelto®) Dabigatran (Pradaxa®) Apixaban (Eliquis®)

Background

The TGA advise they have received 297 adverse drug reports related to the use of rivaroxaban (20), warfarin (23) and dabigatran (258) between May 2011 and September 2011. Many of these were bleeding events.

The TGA notes that some bleeding events with dabigatran have occurred in patients during the transition from warfarin to dabigatran, and in patients on the lower recommended dose.

The TGA has released safety information about Dabigatran (see <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm>)

The newer anticoagulants have no specific reversal agent, unlike warfarin (reversed with vitamin K and plasma/factor concentrates)

Risk Factors

Risk factors to be considered when using all oral anticoagulants include:

- renal impairment;
- older age and /or low body weight; (elderly patients are at significant risk of bleeding)
- other medications may reduce clearance and increase plasma levels of some agents including p-glycoprotein inhibitors (amiodarone, verapamil), CYP3A4 inhibitors (eg macrolides, azoles, protease inhibitors).

Steps to minimise risk

- Patients receiving these newer oral anticoagulants have an increased risk of bleeding and should not routinely be given other anticoagulants (including heparin or low molecular weight heparins).
- Patients stable on warfarin may not benefit from switching to a newer oral anticoagulant.
- Any suspicion of moderate to severe bleeding requires a consultation with senior medical staff or haematologist or, if unavailable, through the NSW Poisons Information Centre at www.chw.edu.au/poisons/ or by calling 131126.
- Assess renal function before commencing therapy. Calculate creatinine clearance because small body mass will disguise poor renal function if eGFR is used.
- Ensure prescribers recognise the newer agents as anticoagulants and understand the risks.
- Check for drug interactions. Great caution should be used if prescribing antiplatelet agents and NSAIDS with these agents.
- Refer to the relevant product information for specific advice on perioperative management of patients.

Suggested Actions by Local Health Districts/ Networks

1. Ensure that this Safety Notice and attachments are distributed to all relevant stakeholders including GP's.
2. Report suspected adverse drug reactions to the TGA at adr.reports@tga.gov.au



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	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Warfarin (Coumadin®, Marevan®)
Anticoagulant action	Competitive reversible direct thrombin inhibitor	factor Xa inhibitor	Factor Xa inhibitor	Inhibits synthesis of vitamin K-dependent clotting factors, proteins C and S.
TGA approved Indication	Prevention of VTE post major orthopaedic surgery of lower limb Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	Prevention of VTE post major orthopaedic surgery of lower limb	Prevention of VTE after elective total hip or knee replacement surgery.	Treatment and prevention of VTE Prevention of embolism in prosthetic heart valves Prevention of stroke with previous MI and increased embolic risk Non-valvular AF with risk of stroke or systemic embolism.
Use in renal impairment	Increased plasma levels and haemorrhagic risk in moderate renal impairment (30-50mL/min CrCL) Contraindicated in severe renal impairment (CrCL < 30mL/min)	Increased plasma levels and haemorrhagic risk in moderate and severe renal impairment Contraindicated in severe renal impairment (CrCL <15mL/min)	Increased plasma levels and haemorrhagic risk in moderate renal impairment (15-29mL/min CrCL) Contraindicated in severe renal impairment (CrCL <15mL/min)	No adjustment required
Drug Interactions	Proton pump inhibitors reduce absorption Possible interactions with P-glycoprotein inhibitors and inducers	Strong inhibitors of both CYP3A4 and P-glycoprotein's may lead to reduced hepatic and renal clearance significantly increased systemic exposure of rivaroxaban.	CYP 3A4 inhibitors and p-glycoprotein inhibitors and inducers (eg rifampicin, phenytoin, carbamazepine, phenobarbitone or St. John's Wort). NSAIDs and anticoagulants	Numerous – See product information or AMH
Reversal agent	nil	nil	nil	Immediate reversal with plasma or factor concentrate Reversal within hours of Vitamin K

Source: NSW Therapeutic Advisory Group

Futher Information

1. TGA Safety Advisory October 2011 Dabigatran: risk of bleeding relating to use <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm>
2. NPS RADAR Reports: Dabigatran August 2011, April 2010, Rivaroxaban Aug 2009 http://www.nps.org.au/health_professionals/publications/nps_radar/view_radar_articles_by_active_ingredient
3. Australian Prescriber Volume 33, Number 2 April 2010
4. New Zealand Government: PHARMAC <http://www.pharmac.govt.nz/healthpros/MedicineInformation/Dabigatran>
5. MIMS Online: Dabigatran Etexilate, Full Product Information. 29/4/11. Accessed 26th Sept 2011
6. MIMS Online: Rivaroxaban, Full Product Information. 30/7/10. Accessed 29th Sept 2011
7. Apixaban TGA approved Product Information 21 July 2011 <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-03072-3>
8. Australian Medicines Handbook: July 2011 Edition
9. Brighton T. New oral anticoagulant drugs – mechanisms of action. Aust Prescr 2010;33:38-41