Canterbury District Health Board
Te Poari Hauora o Waitaha

Clinical Pharmacology Bulletin

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Oral Anticoagulants – Rivaroxaban and Dabigatran

Rivaroxaban (Factor Xa inhibitor), dabigatran etexilate (direct thrombin inhibitor), or warfarin (vitamin K epoxide reductase inhibitor) can be used as oral anticoagulants for most indications. Warfarin remains first line for patients with mechanical heart valves or severe chronic kidney disease.

Indications: Rivaroxaban and dabigatran are licensed for:

- Thromboprophylaxis in non-valvular AF patients at moderate to high risk (e.g. congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke/transient ischaemic attack)
- Treatment of deep vein thrombosis (DVT)
- Prevention of recurrent venous thromboembolism (VTE)
- Thromboprophylaxis after total knee/hip replacement

Rivaroxaban and dabigatran have not been trialled head-to-head or with other new anticoagulants.

Rivaroxaban is available as 10 mg, 15 mg, and 20 mg tablets.

Dabigatran is available as 75 mg, 110 mg, and 150 mg capsules.

Mechanism of action: Rivaroxaban inhibits Factor Xa, a key enzyme in the coagulation system that converts prothrombin to thrombin, while dabigatran inhibits thrombin. These actions of rivaroxaban and dabigatran reduce clot formation and consequent thrombo-occlusive events.

Pharmacokinetics: Rivaroxaban has high oral bioavailability (F >80%).Rivaroxaban is partially renally cleared (~30%), with the remainder hepatically cleared (~30%, via cytochrome (CYP) enzymes, such as CYP 3A). Rivaroxaban is also a substrate of the efflux transporter P-glycoprotein (P-gp). Rivaroxaban has an average half-life of approximately 7 hours.

Dabigatran etexilate has low oral bioavailability (F 0.07). Following absorption dabigatran etexilate is rapidly and completely metabolised to dabigatran (active form). Dabigatran is renally cleared (> 80%), and has an average half-life of approximately 15 hours.

Factors affecting pharmacokinetics: Rivaroxaban serum concentrations are altered by drugs that inhibit/ induce liver enzymes or P-gp, and in renal impairment. Avoid drugs that are major inhibitors/ inducers of both CYP 3A enzymes and P-gp (see the Pink Book) or call Medicines Information Service.

Dabigatran is affected by drugs that inhibit/ induce P-gp. P-gp inhibitors (e.g. ketoconazole) can increase fractional oral bioavailability and consequently serum concentrations of dabigatran. Avoid major P-gp inhibitors, else seek guidance from Medicines Information Service. Reduce doses in patients with creatinine clearance less than 80 mL/min and avoid in patients with creatinine clearance less than 30 mL/min.

Monitoring: For both drugs periodically monitor renal function. Coagulation tests and drug concentrations can be monitored, but seek guidance from haematology or Medicines Information Service.

Standard Doses:

Rivaroxaban

- 20 mg daily
- Post-orthopaedic surgery:10mg daily for 5 weeks (hip) or 2 weeks (knee)

Dabigatran

- 150 mg Q12H
- Patients with moderate renal impairment 110 mg Q12H

Adverse effects: The most common non-bleeding adverse effects of rivaroxaban and dabigatran are gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, dyspepsia and abdominal pain).

Management of bleeding:
For both standard treatment measures should be instituted (e.g. compression, surgery, fluid replacement, blood products (e.g. packed red cells, fresh frozen plasma or platelets)). Phytomenadione (vitamin K) is not useful.

Rivaroxaban

There is no specific antidote available currently in New Zealand. The manufacturer advises prothrombin complex concentrate could be considered, although data on use is limited.

Rivaroxaban is usually cleared within 24-48 hours depending on renal and hepatic function.

Dabigatran (see Hospital HealthPathways)

Idarucizumab (high-cost monoclonal antibody directed against dabigatran) is used in life threatening or uncontrolled bleeding, or for reversal of anticoagulant for emergency surgery or urgent procedures.

Dabigatran is usually cleared within 48-72 hours depending on renal function.

Repacking into compliance packaging
Due to limited information available on the stability of medicines repacked into compliance packaging, only repack medicines if the benefits of compliance packaging outweigh the risk of the medicine being less stable in compliance packaging.

Rivaroxaban	• No published studies assessing chemical stability • Tablets are physically stable when repackaged and stored for 4 weeks at room temperature.
Dabigatran	• Stable for up to 28 days if stored at or below 25 °C. • At high temperatures and humidity the shelf life of should be reduced to 14 days, or packs stored in a refrigerator.

For further information, please see repackaging dabigatran bulletin.