PostScriptExtra

NHS Greater Glasgow and Clyde

NEW ORAL ANTICOAGULANTS

SUMMARY BULLETIN

No. 20(S), Oct 2012◆ Produced by NHS Greater Glasgow and Clyde Medicines Information Service

- There are three new oral anticoagulants licensed in the UK, rivaroxaban, dabigatran and apixaban.
- All three agents are licensed for the prevention of venous thromboembolism (VTE) in hip and knee replacement surgery. Rivaroxaban is the only agent on the total Formulary for this indication.
- Rivaroxaban and dabigatran are licensed for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). Both are on the total Formulary for this indication with restrictions.
- In AF, preference of rivaroxaban or dabigatran over warfarin for practical rather than clinical reasons is non-Formulary.
- Rivaroxaban is also licensed for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT/pulmonary embolism (PE). It is on the Formulary as an alternative to warfarin when the intended treatment duration is 3 to 6 months.

Introduction

There are three new oral anticoagulants licensed in the UK. The direct thrombin inhibitor, dabigatran and the two direct factor Xa inhibitors, rivaroxaban and apixaban. Apixaban is non-Formulary and should not routinely be prescribed in NHS Greater Glasgow & Clyde (NHSGGC). Rivaroxaban and dabigatran are on the Formulary for specific indications and should only be prescribed according to the Formulary restrictions.

What are the new oral anticoagulants licensed for?

Dabigatran is the only oral direct thrombin inhibitor currently licensed in the UK. It is licensed for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery (THR) or total knee replacement surgery (TKR). It is also licensed for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more risk factors (refer to manufacturer's summary of product characteristics (SPC) for further information).

Rivaroxaban is licensed for the prevention of VTE in adult patients undergoing elective THR or TKR surgery. It is also licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors (refer to SPC for further information) and for the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Apixaban is licensed for the prevention of VTE in adults who have undergone elective THR or TKR.

	Rivaroxaban	Dabigatran	Apixaban
Prevention of VTE following hip or knee replacement surgery	On total Formulary with restrictions	Non-Formulary	Non-Formulary
Prevention of stroke and systemic embolism in AF	On total Formulary with restrictions	On total Formulary with restrictions	–
Treatment of DVT and prevention of recurrent DVT and PE	On total Formulary with restrictions	–	–

NB. New indications for these agents are at different stages of development and therefore they may be licensed for additional indications in the near future.

Place in therapy

Prevention of VTE following hip and knee replacement surgery

Rivaroxaban is on the total Formulary restricted to specialist use only in accordance with local protocol. A small proportion of patients may require thromboprophylaxis with rivaroxaban following THR or TKR. In these cases follow orthopaedic and/ or haematology consultant recommendations. Full supply of rivaroxaban is dispensed from the hospital pharmacy.

Dabigatran and ***apixaban*** are non-Formulary for this indication because the formulary decision was that the medicines do not represent sufficient added benefit to rivaroxaban, which is already on the Formulary.

Prevention of stroke and systemic embolism in AF

Dabigatran and ***rivaroxaban*** are on the total Formulary for this indication restricted to patients currently receiving warfarin who have poor INR control despite evidence that they are complying, patients with allergy or intolerable side effects from coumarin anticoagulants or for patients for whom warfarin has been clinically excluded as a therapeutic option but anticoagulation is deemed safe and appropriate. **Preference over warfarin for practical rather than clinical reasons remains non-Formulary**. Further guidance has been produced by the Heart MCN and is available on StaffNet via Info Centre/ Policies, Procedures and Guideline Documents/ NHSGGC Clinical Guideline Electronic Resource Directory.

Which new oral anticoagulant should be prescribed for the prevention of stroke and systemic embolism in AF if indicated?

There are no studies comparing ***rivaroxaban*** and ***dabigatran***. Dabigatran, but not rivaroxaban, was shown to be superior to warfarin in the pivotal studies for AF although rivaroxaban was shown to be non-inferior. Head to head studies would be required to demonstrate whether there is a real difference between these agents.

Dabigatran and rivaroxaban have similar cautions and contraindications. Refer to the SPCs for full information. There is a slight difference in the recommendations for use in renal impairment. Dabigatran is contraindicated in patients with severe renal impairment, (creatinine clearance (CrCl) < 30 ml/min), and rivaroxaban is contra-indicated when CrCl < 15 ml/min.

Rivaroxaban can be considered for inclusion in a dosette box to aid compliance, however, dabigatran is not suitable for storing out with the original container.

Treatment of DVT and prevention of recurrent DVT and PE

Rivaroxaban is on the total Formulary for this indication. It is restricted to use in accordance with local guidance for patients requiring anticoagulation where the intended duration of anticoagulation (at the outset) is determined to be 3 to 6 months. **Where indefinite duration is indicated, the treatment of choice should be a low molecular weight heparin followed by warfarin.**[2] Patients suitable for rivaroxaban, should be treated with dalteparin until the diagnosis has been objectively confirmed. Rivaroxaban should be started 22-24 hours after the last dose of dalteparin. The initial 21 days of therapy is dispensed from hospital pharmacy. Further guidance has been produced by the Thrombosis Committee and is available on StaffNet.

Can rivaroxaban be prescribed for the treatment of acute PE?

Rivaroxaban is not currently licensed for the treatment of acute PE, however, a licence submission has been made to the European Medicines Agency and therefore, it may be licensed for this indication in the near future.

Safety

What monitoring is required for these agents?

No blood monitoring is required for any of the new oral anticoagulants and this may be an advantage compared to warfarin. Dabigatran is contraindicated in patients with CrCl < 30 ml/min, therefore, renal function should be assessed in all patients before starting dabigatran and monitored at least once a year in patients older than 75 years or those with a suspected decline in renal function. For rivaroxaban, caution is required in patients with CrCl < 30 ml/min and it is contraindicated when CrCl < 15 ml/min.

How safe are the new agents and what is the bleeding risk?

The long term safety of the new oral anticoagulants is currently unknown. Published studies to date show rivaroxaban and dabigatran have a similar overall major bleeding risk to dose-adjusted warfarin and enoxaparin (with the exception of dabigatran 110 mg BD which was associated with less major bleeding than warfarin in patients with AF). A meta-analysis and systematic review of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with AF reported that the new agents were more efficacious for the prevention of stroke and systemic embolism than warfarin and were associated with a significant reduction in the risk for intracranial bleeding. The meta-analysis was inconclusive with respect to major bleeding and GI bleeding due to wide confidence intervals. The risk for MI was similar between the new agents and warfarin.

What about reversal?

There is no antidote to any of the new agents and this is a major concern. Refer to the NHSGGC Therapeutics – A Handbook for Prescribing in Adults and contact your local haematologist for advice on reversal of new anticoagulants.

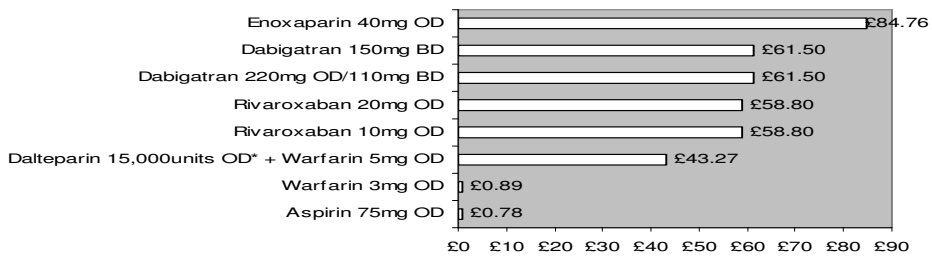
Prescribing advice

Prescribing information can change, therefore, always refer to the latest version of the manufacturer's summary of product characteristics (SPC) at http://emc.medicines.org.uk for full prescribing information including advice on doses, dose reductions, interactions, cautions and contraindications before prescribing any of the new agents.

A number of medicines are contraindicated or should be used with caution with rivaroxaban and dabigatran. When prescribing any new medicines for patients currently on a new anticoagulant, always refer to the SPC to check for interactions.

Refer to the PostScript Extra link on website http://www.ggcprescribing.org.uk for a fully referenced unabbreviated version of this bulletin

Cost for 28 days treatment (Scottish drug tariff/eMIMS Sep 2012)



NB. **Doses shown are for general comparison only and do not imply therapeutic equivalence.** (*Price for dalteparin assumes person weighing 70kg receiving treatment for 5 days)

Produced by NHS Greater Glasgow and Clyde Medicines Information Service ♦ Approved by the Medicines Utilisation Subcommittee of the ADTC ♦ Tel: 0141 211 4407 Email: medinfo@ggc. scot.nhs.uk