







## UPDATE ON ORAL ANTICOAGULATION THERAPY

-  **Oral anticoagulants (OACs) are used for the prevention of embolus in atrial fibrillation and the prevention and treatment of venous thromboembolism**
-  **All OACs are associated with a risk of bleeding; increased risk factors include older age, co-morbidities and concomitant medication**
-  **The new OACs are associated with drug interactions, although less so than warfarin**
-  **Patients on all OACs must be monitored for factors including compliance, renal impairment and adverse events**

### INTRODUCTION

Oral anticoagulants (OACs) are indicated for certain thromboembolic conditions i.e. stroke prophylaxis in non-valvular atrial fibrillation (AF) with additional risk factors and prevention and treatment of uncomplicated venous thromboembolism (VTE). AF is the most common cardiac arrhythmia with approximately 1% of the general population being diagnosed with AF,<sup>1</sup> which is responsible for up to 20% of all ischaemic strokes.<sup>2</sup> The prevalence increases to 4-7% in those aged 65-74 years of age, and to 14-19% in those aged  $\geq 85$  years.<sup>2</sup> VTE is responsible for the death of greater than 500,000 people in Europe each year and is the third leading cause of death from cardiovascular causes after myocardial infarction and stroke.<sup>3</sup> In the UK it is estimated that 25,000 people die from preventable hospital acquired VTE every year;<sup>4</sup> it is a potential complication following major orthopaedic surgery, including total knee replacement or total hip replacement.<sup>5</sup> Acute VTE has an annual incidence of approximately 1-2 per 1,000 persons in the general population.<sup>6</sup>

This, the first of two bulletins will review the pharmacology of the OACs and summarise the evidence for the use of the new OACs (NOACs). A companion bulletin will provide an update on the management of non-valvular AF (NMIC 2013; Vol 19:1).

### BACKGROUND

Anticoagulants are effective for the prevention and treatment of thromboembolic disorders; the decision to use anticoagulants depends on the individual patient; factors such as the risks of thrombosis and bleeding must be taken into account.<sup>4,7-10</sup> Traditional anticoagulants such as low molecular weight heparin, unfractionated heparin and vitamin K antagonists (VKA) [usually warfarin] have several limitations.<sup>3,5,6,11,12</sup> The oral anticoagulant warfarin has several limitations including a narrow therapeutic index, variations in its anticoagulant effect, numerous food and drug interactions and the need for regular monitoring.<sup>5,13-16</sup> Patients on warfarin require regular monitoring of the international normalised ratio (INR) to ensure maximal time in the therapeutic range (TTR).<sup>15,17,18</sup> A high TTR is associated with a lower risk of thromboembolic events and bleeding.<sup>17,18</sup> Studies suggest that the TTR can range from 44-77%, and varies by country and local standards of care.<sup>17-20</sup> Interventions which improve TTR include use of self-monitoring and point of care testing.<sup>20,21</sup>

The limitation of the traditional anticoagulants led to the development of NOACs that target either thrombin or Factor Xa (FXa).<sup>6,16</sup> Ximelagatran was the first oral direct thrombin inhibitor to be authorised; however it was withdrawn in 2006 due to hepatotoxicity.<sup>16</sup> The NOACs (dabigatran etexilate, rivaroxaban and apixaban),<sup>16</sup> have recently been approved for stroke prophylaxis in non-valvular AF and prophylaxis of VTE after elective hip or knee replacement; in addition rivaroxaban is approved for the treatment of VTE.

### PHARMACOLOGY OF ORAL ANTICOAGULANTS

**Warfarin** acts by lowering the levels of the vitamin K-dependent procoagulant proteins including prothrombin and Factors VII, IX, and X, as well as the vitamin K-dependent anticoagulant proteins, protein C, S and Z.<sup>22</sup> It has a slow onset of action. Its effects vary widely between individuals and are influenced by factors including genetic determinants, age and comorbidities.<sup>14</sup> Fluctuations in dietary intake of vitamin K and alcohol and several drug interactions further contribute to inter- and intra-individual variability in the anticoagulant effects of warfarin. Warfarin consists of two isomers which are metabolised by different CYP 450 isoenzymes including CYP1A2, CYP3A4 and CYP2C9.<sup>23,24</sup> The commonest pharmacokinetic interaction with warfarin involves the inhibition or induction of its metabolism.<sup>23</sup>

**Dabigatran etexilate** is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin.<sup>14,25</sup> Dabigatran etexilate is a substrate for the P-glycoprotein (P-gp) transporter; co-administration of potent P-gp inhibitors increases plasma concentrations of dabigatran and co-administration of potent P-gp inducers reduces plasma concentrations of dabigatran.<sup>13,14</sup> As up to 80% of dabigatran is excreted in the urine, there is **potential for drug accumulation in patients with renal impairment**. The half life of dabigatran increases to 18 hours in patients with a creatinine clearance (CrCl) of 30-50 mL/min and to  $> 24$  hours if the CrCl is  $< 30$  mL/min.<sup>14</sup> Dabigatran is contra-indicated in patients with CrCl  $< 30$  mL/min and close clinical surveillance is recommended in patients with renal impairment (dose reduction may be required).<sup>26-28</sup>

**Rivaroxaban** is an active drug which is a direct FXa inhibitor.<sup>13,22</sup> Rivaroxaban is partially metabolised through the CYP 450 system and is a P-gp substrate, potentially leading to several drug interactions.<sup>13,14,29</sup> **One third of rivaroxaban is eliminated unchanged by the kidneys**; the remaining two thirds are metabolised, with half being eliminated renally and the other half eliminated by the faecal route.<sup>30-32</sup> Rivaroxaban is not recommended in patients with CrCl  $< 15$  mL/min and caution is recommended in patients with CrCl = 15-29 mL/min (dose reduction may be required).<sup>30-33</sup>

**Apixaban** is an active drug which is a direct FXa inhibitor.<sup>34</sup> Apixaban is eliminated by several pathways; it is metabolised through CYP 450 3A4 to several metabolites and is a P-gp substrate.<sup>14,29</sup> Up to 50% of apixaban is excreted in the faeces while **27% is excreted via the kidneys**.<sup>14,35</sup> Apixaban is not recommended in patients with CrCl  $< 15$  mL/min and should be used with caution in patients with CrCl = 15-29 mL/min (dose reduction may be required).<sup>35</sup>

Table 1 summarises the pharmacology of the four oral anticoagulants.

**Table 1: Comparative pharmacology of the oral anticoagulants**<sup>22, 26-28,30-35</sup>

| Characteristic   | Warfarin         | Dabigatran etexilate | Rivaroxaban               | Apixaban                  |
|--|------------------|----------------------|---------------------------|---------------------------|
| <b>Target</b>  | Vitamin K enzyme | Thrombin             | Factor Xa                 | Factor Xa                 |
| <b>Prodrug</b>   | No               | Yes                  | No                        | No                        |
| <b>Bioavailability</b>   | 100%             | 6%                   | 60-80%                    | 50%                       |
| <b>Dosing</b>  | Once daily       | Once or twice daily* | Once or twice daily*      | Twice daily               |
| <b>Time to peak effect</b>                                     | 4-5 days         | 1-3 hours            | 2-4 hours                 | 3-4 hours                 |
| <b>Half-life</b>   | 40 hours         | 8-15 hours           | 5-13 hours                | 12 hours                  |
| <b>Renal clearance</b>   | None             | 80%                  | 33%                       | 27%                       |
| <b>Monitoring tests readily available for routine practice</b> | Yes              | No                   | No                        | No                        |
| <b>Interactions</b>  | Multiple         | P-glycoprotein       | CYP 3A4<br>P-glycoprotein | CYP 3A4<br>P-glycoprotein |

\* depending on indication

**Drug interactions:** Patients on warfarin prescribed concomitant medications are at particular risk of drug interactions; increased INR monitoring is advised following changes to concomitant interacting drugs. The NOACs have fewer documented drug interactions than warfarin, however **they are all P-glycoprotein (P-gp) substrates and rivaroxaban and apixaban are metabolised to some degree by the CYP 450 system, leading to potential risks of pharmacokinetic drug interactions.**<sup>25</sup> P-gp inhibitors may increase the absorption of a NOAC, thereby increasing serum concentration, leading to potential toxicity, while P-gp inducers may decrease serum concentrations of the NOACs, potentially resulting in decreased efficacy.<sup>16,29</sup> The lack of a readily available standardised coagulation monitoring method for NOACs poses a challenge in these situations.<sup>6</sup> Table 2 identifies some of the common P-gp inhibitors and inducers.

**Table 2: Common P-glycoprotein inhibitors and inducers**<sup>29</sup>

| P-glycoprotein inhibitors*  | P-glycoprotein inducers  |
|---|--|
| <b>Amiodarone</b><br>Ceftriaxone<br><b>Clarithromycin</b> , erythromycin<br><b>Ciclosporin</b><br>Diltiazem<br>Dipyridamole<br><b>Dronedarone</b><br>Hydrocortisone<br><b>Ketoconazole</b> , itraconazole | Nicardipine, nifedipine<br>Propranolol<br>Quinine<br><b>Quinidine</b><br>Ritonavir, saquinavir, nelfinavir<br>Tamoxifen<br><b>Tacrolimus</b><br><b>Verapamil</b> |
|   | Rifampicin<br>Clotrimazole<br>Phenytoin<br>Phenobarbitol<br>St John's Wort   |

\* potent inhibitors are in bold

**Dabigatran** is contraindicated with ketoconazole, ciclosporin, itraconazole, tacrolimus and dronedarone.<sup>26-28</sup> **Rivaroxaban** or **apixaban** are not recommended in patients receiving treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir).<sup>31-35</sup>

**Pharmacodynamic interactions** may be predicted based on the pharmacology and adverse reaction profile of the NOACs. Co-administration of the NOACs or warfarin with aspirin or other NSAIDs increases the risk of bleeding and the risk is greater with dual antiplatelet therapy.<sup>14</sup> Drug interactions may vary depending on the indication; **the current Summary of Product Characteristics (SmPCs) should be reviewed for full prescribing information.**

## EVIDENCE FROM CLINICAL TRIALS FOR THE NOACS

There have been a number of pivotal trials comparing the NOACs to the traditional anticoagulants (mainly warfarin and/or enoxaparin). The results of these studies form the basis for the authorisation of the NOACs in Europe.<sup>16</sup> Evidence supporting the use of the NOACs in non-valvular AF will be reviewed in the companion bulletin (NMIC 2013;19:1). Table 3 summarises the current licensed indications of the NOACs.

**Table 3: Current licensed indications\* for the new oral anticoagulants**<sup>26-28,30-33,35</sup>

| Indication   | Dabigatran | Rivaroxaban | Apixaban |
|--|------------|-------------|----------|
| Prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors | +          | +           | +        |
| Primary prevention of VTE in adults who have undergone elective total hip or knee replacement surgery                    | +          | +           | +        |
| Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults  |            | +           |          |

\* - the individual Summary of Product Characteristics should be consulted for full prescribing information

## 1. VTE PREVENTION FOLLOWING ORTHOPAEDIC SURGERY

Provided there are no contraindications, prophylactic anticoagulation therapy is standard practice after total knee replacement (TKR) or total hip replacement (THR), with a duration of therapy of 10-14 days and 28-35 days respectively.<sup>4,6</sup> Dabigatran, rivaroxaban and apixaban are authorised for prophylaxis of VTE in patients undergoing elective THR or TKR.<sup>3</sup> The pivotal studies are mainly based on findings from mandatory venography of the legs which is not routinely carried out in clinical practice; also the definitions for bleeding may differ between the different studies.<sup>3</sup>

**Dabigatran etexilate:** Four phase III (pivotal) trials (n=9,521) compared dabigatran 150mg or 220mg once daily to enoxaparin (40mg daily or 30mg twice daily) for the prevention of VTE after TKR or THR surgery.<sup>36-39</sup> The results of three studies concluded that both dabigatran 150mg or 220mg once daily was non-inferior to enoxaparin 40mg once daily for prevention of VTE after THR or TKR, and there was a similar bleeding event profile.<sup>5,6,36-38</sup> In the fourth study, both doses of dabigatran showed inferior efficacy to enoxaparin 30mg twice daily (dose not licensed in Europe) for VTE prevention after TKR.<sup>39</sup>

**Rivaroxaban:** Four phase III trials (n=12,729) compared rivaroxaban 10mg daily to enoxaparin (40mg daily or 30mg twice daily)

for prevention of VTE after TKR or THR surgery.<sup>40-43</sup> The results found that, compared with enoxaparin, rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality after elective THR or TKR surgery. There was an increased trend for major and clinically relevant bleeding with rivaroxaban; this did not reach statistical significance.<sup>12,44</sup>

**Apixaban:** Three phase III trials (n=11,659) compared apixaban 2.5mg twice daily to enoxaparin (40mg daily or 30mg twice daily) for the prevention of VTE after TKR or THR surgery.<sup>45-47</sup> Apixaban was superior to enoxaparin 40mg daily, in two studies for prevention of VTE after TKR and THR surgery, however in one THR study, it failed to prove non-inferiority to enoxaparin 30mg twice daily.<sup>5,6,45-47</sup> There was a trend for less major and clinically relevant bleeding with apixaban; this did not reach statistical significance.<sup>48</sup>

There are no head to head comparisons of the NOACs and it is difficult to compare the trials due to the heterogeneity between the trials.<sup>48</sup>

## 2. TREATMENT AND SECONDARY PREVENTION OF VTE

The current pharmacological standard treatment of acute VTE is rapidly acting parenteral anticoagulants for 5-7 days followed by at least 3 months' treatment with a vitamin K antagonist (generally warfarin).<sup>7</sup> Up to 30% of patients experience recurrent VTE and therefore some patients may require more prolonged OAC treatment;<sup>6</sup> the risks and benefits of continuing treatment should be assessed in the individual patient.<sup>7</sup> Currently rivaroxaban is the only NOAC authorised for the treatment of deep venous thrombosis (DVT) and pulmonary embolus (PE) and the prevention of recurrent DVT and PE in adults.

**Rivaroxaban:** Three phase III trials assessed the efficacy and safety of rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) for VTE treatment compared to enoxaparin and warfarin; the acute DVT treatment trial, the acute PE trial and the study of extended-duration treatment for DVT and PE.<sup>5,44,49,50</sup> Rivaroxaban was found to be non-inferior to enoxaparin/warfarin for the prevention of recurrent symptomatic VTE and the number of major or non-major clinically bleeding events was similar in the two treatment groups.<sup>5,6,44</sup>

Dabigatran etexilate and apixaban are currently not authorised for this indication, however studies are ongoing.<sup>5,51</sup>

## PRACTICAL MANAGEMENT ASPECTS OF THE NOACS

Patients on long-term OACs must be followed up regularly (at least annually) to confirm that clinical factors have not arisen which might alter the risk/benefit ratio between the prevention of thrombosis and risk of bleeding. **Warfarin remains the anticoagulant of choice for many patients including those with mechanical heart valves, valvular AF, severe renal impairment, cancer related VTE and complicated VTE such as patients with recurrent VTE or patients with antiphospholipid syndrome.**<sup>8,10,14,15</sup> Such patients should not be switched from warfarin to a NOAC. Evidence from clinical trial data suggests that the NOACs could simplify management of the prevention and treatment of uncomplicated VTE and for patients with non-valvular AF. The advantages of the NOACs include a rapid onset of action, less drug interactions compared with warfarin and a predictable effect that does not require routine laboratory monitoring of their anticoagulant effect.<sup>5,6,14,15,52</sup> A significant disadvantage of NOACs is the lack of a specific reversal agent (see below) and in addition, there are concerns regarding the risks of bleeding in an unselected population as distinct from a clinical trial setting and regarding the effects of non-adherence on thrombosis risk given the short half-lives of the NOACs.<sup>6,9</sup> **The decision to start a NOAC needs to be individualised to the patient and to the indication for which the patient is being treated.** It is not recommended to routinely switch patients who are well controlled on warfarin to one of the NOACs, as those who have a satisfactory time in the therapeutic INR range seem to benefit little in changing treatment.<sup>15,26</sup>

**The dose of each NOAC varies depending on the different indication; dose reductions may be required for patients including the elderly, those on interacting medications and with renal impairment.**<sup>26-28,30-33,35</sup> Full prescribing information is available in the SmPC. If a NOAC is considered, clinicians should be aware that clinical experience with these agents is still limited, therefore care and vigilance are needed.<sup>9</sup>

**Monitoring:** Early follow-up is essential for all patients on the NOACs to assess adherence and monitor for adverse effects.<sup>14,15,53</sup>

**There is potential for drug toxicity particularly in the elderly, those with renal insufficiency and those on interacting drugs.** There is an increased incidence of dyspepsia with dabigatran, which may lead to discontinuation.<sup>14,29</sup>

**Adverse effects:** The most commonly reported adverse effect with the NOACs is bleeding.<sup>26-28,30-33,35</sup> Even though the NOACs in clinical trials were found to be non-inferior or superior to warfarin in terms of major bleeding, **all anticoagulants have a risk of bleeding.**<sup>29</sup> **Patients who are at high risk of bleeding with the traditional anticoagulants do not have a lower risk of bleeding when using NOACs.**<sup>6</sup> Post marketing bleeding events including fatalities have been reported with the use of dabigatran, the first NOAC to be authorised.<sup>13,25,54,55</sup> These events occurred up to several months after initiation of treatment and risk factors included elderly patients, severe renal impairment and off-label use.<sup>13,15,29,54,56</sup> Post marketing reports of treatment failure with dabigatran have also been reported.<sup>15</sup> These factors should also be considered for rivaroxaban and apixaban.<sup>6,13</sup> Patients with a poor history of compliance may potentially have a higher risk of not achieving a therapeutic effect of the NOACs because of their relatively short half-life.<sup>6</sup> NOACs have been in use only for a few years and the emergence of further serious adverse effects is still a possibility.<sup>26</sup>

**Renal Function:** All NOACs are excreted by the kidneys to some extent. **Renal function should be assessed prior to initiating treatment, during treatment at least annually and if a decline in renal function is suspected** (e.g. hypovolaemia, dehydration) and with certain co-medications such as P-gp inhibitors.<sup>26-28</sup> Creatinine clearance can be calculated from the Cockcroft and Gault formula (figure 1).<sup>57</sup> In particular, caution is needed in elderly patients who may have unpredictable deteriorating renal function.<sup>16</sup> The individual SmPC should be consulted, as the dose of each NOAC varies depending on the indication and the severity of renal impairment.

**Figure 1: Cockcroft and Gault formula for calculation of creatinine clearance<sup>57</sup>**

$$\text{Estimated Creatinine Clearance in mL/minute} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}}$$

Age in years

Weight in kilograms; use ideal body-weight

Serum creatinine in micromole/litre

Constant = 1.23 for men; 1.04 for women

**Advice to patients:** All patients on OACs should be educated about the risk of bleeding complications associated with all OACs and informed of warning symptoms such as red or dark brown urine or stool, severe headache, unusual weakness or excessive menstrual loss.<sup>58-61</sup> **They should be informed of the importance of adhering to the precise dosage schedule of their medicine and of the risk of lack of efficacy (such as risk of stroke or VTE) if they are not compliant.**



**Switching:** Occasionally, patients on warfarin or parenteral anticoagulants may require a switch to NOACs or vice versa. The individual SmPC should be consulted and specialist advice from a local clinical haematology service is recommended for these situations.<sup>26-28,30-33,35</sup>

**Laboratory monitoring** for anticoagulant effect is not required for routine follow-up of NOACs, however in certain situations such as a patient who has developed renal failure, overdose, emergency surgery or major bleeding, anticoagulation monitoring may be useful.<sup>5,6,11,26</sup> Currently **standardised assays for the measurement of serum drug concentration of NOACs are available in specialist coagulation laboratories** but are not readily available in clinical practice. The prothrombin time (PT) and activated partial thromboplastin time (APTT) are both prolonged in the presence of direct thrombin inhibitors (dabigatran) or FXa inhibitors (rivaroxaban and apixaban).<sup>62-64</sup> The INR should not be used in the care of these patients, but general laboratories may report the INR and it is expected to be abnormal in the presence of therapeutic NOAC drug levels. **The degree of prolongation of the PT or APTT does not correlate with the amount of NOAC present.**<sup>62-64</sup> However a normal APTT in a patient on dabigatran and a normal PT in a patient on rivaroxaban indicates that no clinically significant drug concentration is present.<sup>62-64</sup>

**Surgery and invasive procedures:** Patients on NOACs who undergo surgery or invasive procedures are at increased risk of bleeding. In general, for patients with normal renal function the NOACs should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding and at least 48 hours prior to procedure for those with a high risk of bleeding.<sup>26-28,30-33,35</sup> Specific discontinuation rules for dabigatran are summarised in table 4.<sup>26-28</sup> The NOAC may be restarted 48-72 hours after a procedure with a high risk of bleeding and 24 hours after a procedure with a low risk of bleeding, as long as adequate haemostasis has been established.<sup>64</sup>

**Table 4: Discontinuation rules for dabigatran before invasive or surgical procedures<sup>26-28</sup>**

| Renal Function<br>(Creatinine Clearance in ml/min) | Estimated half-life<br>(hours) | Time to stop dabigatran before elective surgery |                                |
|--|--------------------------------|---|--------------------------------|
|  |                                | High risk of bleeding or major surgery          | Standard risk                  |
| ≥ 80   | Approx. 13                     | 2 days before                                   | 24 hours before                |
| ≥ 50 - < 80  | Approx. 15                     | 2 - 3 days before                               | 1 - 2 days before              |
| ≥ 30 - < 50  | Approx. 18                     | 4 days before                                   | 2 - 3 days before (> 48 hours) |

**Reversibility:** One of the concerns regarding the NOACs is the lack of a specific antidote for emergency situations.<sup>14,15,26,53</sup> The NOACs have short half-lives and in non-acute situations, when the drug is stopped, drug concentrations will decline relatively rapidly in patients with normal renal function.<sup>29</sup> Reversibility in emergency situations such as trauma, life-threatening bleeding or emergency surgery or in patients with severe renal insufficiency is unclear.<sup>29</sup> The management of bleeding should be individualised to the patient based on the location and severity of the haemorrhage; the initiation of appropriate treatment such as surgical haemostasis or transfusion support should be considered.<sup>64</sup> In the setting of overdose activated charcoal may be considered to decrease the absorption of the NOACs.<sup>64-66</sup> Dabigatran can be dialysed, however rivaroxaban and apixaban are not expected to be dialysable due to their high levels of protein binding.<sup>14,15,26</sup> There is some evidence to support the use of activated prothrombin complex concentrates (aPCCs) [Feiba®] for reversal of dabigatran or four-factor PCC [Octaplex®] as reversal agents for rivaroxaban and apixaban but data is limited (off-label use).<sup>62,64-66</sup>

## SUMMARY

- It is not recommended to routinely switch patients who are well controlled on warfarin to one of the NOACs
- NOACs should not be prescribed for off-label indications
- Prescribing information on dabigatran, rivaroxaban and apixaban may vary depending on the indication in terms of the dosage, the contraindications, the precautions for use, use in renal impairment and drug interactions; prescribers should ensure that the correct section of the relevant SmPC is consulted
- All the NOACs are excreted by the kidneys; renal function needs to be evaluated at baseline and on an ongoing basis as it impacts on the dose and safety profile of NOACs
- All anticoagulants, including the NOACs, are associated with a risk of bleeding
- Patients at increased risk of bleeding include the elderly, those with renal impairment, co-administration of certain drugs and other risk factors (e.g. coagulopathy, active gastrointestinal disease and recent trauma)
- Patients should be educated on the risk of bleeding associated with all OACs and of the importance of adhering to treatment
- All patients on NOACs should be monitored for adverse effects on an ongoing basis
- All the NOACs are P-glycoprotein substrates; rivaroxaban and apixaban are metabolised by the CYP 450 system, leading to potential risks of drug interactions. Check the relevant SmPC for details of specific interactions
- Care is required when switching from traditional anticoagulants to NOACs and vice versa; the individual SmPC should be consulted and specialist advice is recommended
- There are no standardised tests readily available in routine practice for monitoring the anticoagulant effects of the NOACs
- There are no specific antidotes for NOACs
- If a NOAC is considered, clinicians should be aware that clinical experience with these agents is still limited, therefore care, vigilance and further information on their effectiveness in clinical practice are needed
- **In Ireland, approval for individual patient reimbursement for a NOAC must be obtained from the HSE through the primary care reimbursement service (PCRS). Application forms are available online at:**  
<http://www.sspcrs.ie/libr/html/OralAnticoagulantIndividualReimbursemenApplication.pdf>

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List of references available on request. Date of preparation: February 2013

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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