Non-Vitamin K Antagonist oral anticoagulants (NOACs) for the treatment and prevention of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

NOACs are recommended as an option for treating and/or preventing recurrent DVT and/or PE where an oral anticoagulant is indicated following specialist initiation.

NICE TAs 261\(^1\) and 287\(^2\) (rivaroxaban), 327\(^3\) (dabigatran), 341\(^4\) (apixaban) and 354\(^5\) (edoxaban) recommend NOACs as an option for treating and/or preventing recurrent DVT and/or PE in adults. **Treatment with dabigatran and edoxaban should be preceded with at least 5 days of parenteral anticoagulant.** Parenteral anticoagulation pre-treatment is not required with rivaroxaban or apixaban. It is recommended that the decision to prescribe warfarin or a NOAC should be taken after consideration of the benefits and risks of the treatment options.

The Pan Mersey APC recommends that NOACs should especially (but not exclusively) be considered for use in those circumstances where warfarin is not suitable due to contraindications (including impossibility of monitoring of warfarin), intolerance or when the full treatment course would be with a parenteral anticoagulant. In patients with active cancer, NICE acknowledged the lack of evidence comparing any NOAC with extended treatment with low molecular weight heparin (LMWH) and concluded that it was not possible to make a specific recommendation for this patient group.

Treatment duration is the responsibility of the consultant/specialist initiating treatment and should be clearly communicated to the patient’s GP.

Prescribers should be aware that dabigatran is the only NOAC with a specific antidote available. There is currently no specific antidote available for any of the other NOACs. This should be taken into account when deciding whether or not to initiate therapy with a NOAC.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.
**Apixaban tablets (Eliquis®▼) for the treatment and prevention of Deep Vein Thrombosis and/or Pulmonary Embolism**

**EFFECTIVENESS**
A 6-month study has demonstrated a fixed dose regimen of apixaban alone was noninferior to conventional treatment with enoxaparin and dose adjusted warfarin for the treatment of acute VTE and was associated with statistically significant less bleeding. Reduction in major bleeding with apixaban was paralleled by a decrease in clinically relevant non major bleeds compared to conventional warfarin treatment. Efficacy and reduction in major bleeding with apixaban remained consistent across the entire study population, including those people on warfarin treatment who achieved a high percentage time in therapeutic range (TTR) (exceeding 60%).

Extended treatment (up to 12 months) with apixaban has not been directly compared to warfarin for the secondary prevention of VTE. Although continued efficacy was demonstrated without increasing risk of major bleeds compared to placebo this was in a population considered to be in clinical equipoise (uncertainty regarding need for continued anticoagulation). It is unclear how generalisable these results are to current UK clinical practice where anticoagulation is generally continued only when clinical benefit clearly outweighs risk of harm.

**SAFETY**
In the 2 pivotal phase III studies (AMPLIFY [acute treatment of VTE] and AMPLIFY-EXT [secondary prevention of VTE]) major bleeding was the primary safety outcome and the composite of major bleeding and clinically relevant non major bleeding a secondary safety outcome. Major bleeding was defined as overt bleeding that was associated with a decrease in haemoglobin of 2g per decilitre or more, leading to a transfusion of 2 or more units of red cells. Clinically relevant non major bleeding was defined as overt major bleeding that did not meet the criteria for major bleeding but that was associated with need for medical intervention, unscheduled contact with a clinician, interruption or discontinuation of study drug, or impairment of activities of daily living.

In AMPLIFY^6 major bleeding and the composite of major bleeding and clinically relevant non major bleeding was statistically significantly lower with apixaban compared to enoxaparin/warfarin. There were also a lower number of intracranial and gastrointestinal bleeds in patient taking apixaban compared to those taking warfarin.

In AMPLIFY-EXT^7 there were similar rates of major bleeding and clinical relevant non major bleeding between apixaban and placebo.

There is currently no specific, established antidote to apixaban. However data suggest reversibility with prothrombin complex concentrate (PCC)^8

**COST**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Cost per patient (ex VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 1st Month</td>
<td>£70.30</td>
</tr>
<tr>
<td>Apixaban after 1st month</td>
<td>£694 per year</td>
</tr>
<tr>
<td>Enoxaparin 1.5mg/kg for first 9 days (120mg daily assumed) with dose adjusted warfarin started on day 1 (based on 6mg average daily warfarin dose and 6 INR visits at £20 per visit) for 6 months</td>
<td>£428 per course</td>
</tr>
<tr>
<td>Dose adjusted warfarin (based on 6mg average daily dose and 6-12 INR visits at £20 per visit)</td>
<td>£144-£264 per year</td>
</tr>
</tbody>
</table>

Based on the NICE costing template developed for TA 341 estimated demand would be up to 120 patients per 100,000 population at year 5 (steady state) who will be treated with a NOAC rather than LMWH/warfarin.

**PATIENT FACTORS**
Duration of therapy with apixaban for the prevention of recurrent VTE should be individualised following careful assessment of the chance of clinical benefits versus the risk of harm from bleeding.

Patients with elevated liver enzymes (ALT/AST>2 x upper limit normal [ULN]) or total bilirubin ≥1.5 x ULN apixaban should be used with caution. Prior to initiating treatment a liver function test should be performed.

In patients with concomitant conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risk should be made before combining this therapy.

Consult SPC for further details at: [www.medicines.org.uk](http://www.medicines.org.uk)

**PREScribing AND iMPLEMENTATION INFORMATION**
- Treatment should be started by a specialist in the management of VTE. Following initiation, prescribing can be continued in primary care by the GP. Initial supply of apixaban should be made by secondary care and include the loading dose (first 7 days) and start of maintenance dose.
- Duration of treatment must be communicated to the GP on initiation of treatment.
- Recommended starting dose of apixaban for the acute treatment of VTE is 10mg twice daily for 7 days followed by 5mg twice daily for 6 months. If treatment is to be continued beyond 6 months for the prevention of recurrent VTE, apixaban should be reduced to 2.5 mg twice daily.
- Renal function should be assessed in all patients before starting apixaban and at least once a year and more frequently in those with a suspected decline in renal function. Apixaban is not recommended if creatinine clearance is <15ml/min.
- When switching from warfarin to apixaban, stop warfarin (or other vitamin K antagonist [VKA]) and start apixaban when the INR is <2.0.
- When switching from apixaban to warfarin, continue apixaban for at least 2 days after beginning warfarin (or other VKA) or until INR > 2.0.
- When switching from parenteral anticoagulant to apixaban, start apixaban at the time next scheduled dose of parenteral therapy would be administered. These agents should not be given simultaneously.
- When switching from apixaban to parenteral anticoagulation, start parenteral therapy at the time next scheduled dose of apixaban would be administered. These agents should not be given simultaneously.
- A missed dose of apixaban should be taken immediately and then twice daily intake continued as before.
- Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).
**EFFECTIVENESS**

Two trials have compared dabigatran and warfarin in the active treatment of VTE (RE-COVER 10,11 and RE-COVER 2 12). Both studies were multicentre, randomised, double blind, double dummy controlled studies with identical design. The studies included 5153 patients with confirmed acute, symptomatic VTE randomised to either dabigatran 150mg bd or dose adjusted warfarin (INR 2-3). Patients also received at least 5 days parenteral anticoagulation prior to dabigatran or until the INR was 2-3 with warfarin. Treatment was for 6 months. The primary outcome of recurrent, symptomatic VTE and VTE related death occurred in 60 patients (2.4%) in the dabigatran arm and 55 patients (2.2%) in the warfarin arm (HR 1.44 95% CI 0.78-2.64 p=0.01 for non-inferiority). Time in therapeutic range (TTR) for patients treated with warfarin was 57-60%.

Two further studies have evaluated the use of dabigatran in the secondary prevention of VTE. RE-MEDY 12 was a randomised, double blind study comparing dabigatran 150mg bd with warfarin (INR 2-3) in 2866 patients with confirmed acute VTE treated with anticoagulation for 3-12 months. The primary endpoint of recurrent, symptomatic and objectively confirmed VTE or death associated with VTE occurred in 26 patients (1.8%) in the dabigatran arm and 18 patients (1.3%) in the warfarin arm (HR 1.44 95% CI 0.78-2.64 p=0.01 for non-inferiority). TTR for patients treated with warfarin was 62%. RE-SONATE 13 was a randomised, controlled study comparing dabigatran 150mg bd with placebo in 1353 patients who had completed 6-18 months of treatment with a vitamin K antagonist for confirmed, acute VTE. The primary endpoint of recurrent, symptomatic and objectively confirmed VTE or death associated with VTE occurred in 3 patients (0.4%) in the dabigatran arm and 37 patients (5.6%) in the placebo arm (HR 0.08 95% CI 0.02-0.25 p=0.001 for superiority).

### COST PER PATIENT*

<table>
<thead>
<tr>
<th><strong>Cost per patient (ex VAT)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran 1st month (including LMWH)</strong></td>
</tr>
<tr>
<td><strong>Dabigatran after 1st month</strong></td>
</tr>
<tr>
<td><strong>Enoxaparin 1.5mg/kg for first 9 days (120mg daily assumed) with dose adjusted warfarin started on day 1 (based on 6mg average daily warfarin dose and 6 INR visits at £20 per visit) for 6 months</strong></td>
</tr>
<tr>
<td><strong>Dose adjusted warfarin (based on 6mg average daily dose and 6-12 INR visits at £20 per visit)</strong></td>
</tr>
</tbody>
</table>

**SAFETY**

In the RE-COVER studies 10,11 major bleeding occurred in 1.4% of patients in the dabigatran arm and 2.0% in the warfarin arm (HR 0.73 95% CI 0.48-1.11) and major bleeding or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran arm and 8.5% in the warfarin arm (HR 0.62 95% CI 0.5-0.76). Intracerebral haemorrhage was similar in both arms (0.1% with dabigatran and 0.2% with warfarin).

In the RE-MEDY study 12 major bleeding occurred in 0.9% of patients in the dabigatran arm and 1.8% in the warfarin arm (HR 0.52 95% CI 0.27-1.02) and major bleeding or clinically relevant bleeding occurred in 5.6% of patients in the dabigatran arm and 10.2% of those in the warfarin arm (HR 0.54 95% CI 0.41-0.71 p<0.001). Intracerebral haemorrhage was similar in both arms (0.1% with dabigatran and 0.3% with warfarin).

In the RE-SONATE 13 study major or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran arm and 1.8% of those in the placebo arm (HR 2.92 95% CI 1.52-5.6 p=0.001).

In the RE-COVER studies and the RE-MEDY study, dyspepsia occurred at a higher rate with dabigatran compared with warfarin. There is a specific antidote available for dabigatran (idarucizumab).

**PATIENT FACTORS**

Patients aged > 80 years should have a dose reduction to 110mg bd due to an increased risk of bleeding. The dose should also be reduced to 110mg bd in patients taking verapamil. Consider 110mg bd when the thromboembolic risk is low and bleeding risk high or if the patient weighs <50Kg. In gastritis, oesophagitis or gastroesophageal reflux consider 110mg bd.

Dabigatran is contraindicated in patients with hepatic impairment or with severe renal impairment (Creatinine clearance (CrCl) <30ml/min). It is contraindicated in people who are taking ketoconazole, itraconazole, dronedarone, tacrolimus or ciclosporin.

Consult SPC for more details at: www.medicines.org.uk

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**PRESCRIBING INFORMATION**

- **Treatment** should be started by a specialist in the management of VTE. Following initiation, prescribing can be continued in primary care by the GP. **Initial supply of dabigatran should be made by secondary care.**
- **Duration of treatment must be communicated to the GP on initiation of treatment.**
- **Patients** should receive at least 5 days treatment with a parenteral anticoagulant before starting dabigatran.
- The recommended starting dose of dabigatran for the treatment or prevention of VTE in patients <80 years is 150mg bd. In patients > 80 years or in those also taking verapamil, the dose should be reduced to 110mg bd.
- Renal function should be assessed in all patients before starting dabigatran and at least once a year and more frequently in those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (CrCl <30ml/min).
- When switching from warfarin to dabigatran, stop warfarin and start dabigatran when the INR is below 2.0.
- When switching from dabigatran to warfarin, start warfarin 3 days before dabigatran is discontinued if CrCl>50ml/min and 2 days before dabigatran is discontinued if CrCl is 30-50ml/min.
- When switching from parenteral anticoagulant to dabigatran, start dabigatran 0-2 hours before next dose of LMWH is due or at the same time as the continuous intravenous infusion of unfractionated heparin is stopped.
- When switching from dabigatran to parenteral anticoagulant, wait 12 hours after the last dose of dabigatran before starting the parenteral anticoagulant.
- A missed dose of dabigatran can be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.
- Dabigatran is not suitable for use in monitored dosage systems.
- **Patients** should be issued with a Patient Alert Card (available from manufacturer).
EFFECTIVENESS

8292 patients were enrolled into a multicentre, randomised, double blind non-inferiority study comparing edoxaban 60mg daily (reduced to 30mg daily if body weight <60Kg or CrCl 30-50ml/min) with dose adjusted warfarin (INR 2-3) following at least 5 days of parenteral anticoagulant therapy (Hokusai-VTE)\textsuperscript{16}. The study drug was continued for 3-12 months. For those patients receiving warfarin, the INR was within the therapeutic range for 63.5% of the time.

The primary efficacy outcome was the incidence of symptomatic recurrent VTE (composite of DVT or non-fatal or fatal PE). Edoxaban had non-inferior efficacy with respect to the primary efficacy outcome compared with warfarin (3.2% with edoxaban and 3.5% with warfarin HR 0.89 95% CI 0.7-1.13 p<0.001 for non-inferiority).

SAFETY

In the Hokusai-VTE study\textsuperscript{15}, the principal safety outcome was the incidence of clinically relevant bleeding, defined as a composite of major or clinically relevant non-major bleeding. Major bleeding was defined as overt bleeding that was associated with a decrease in haemoglobin of 2g per decilitre or more, leading to a transfusion of 2 or more units of red cells. Clinically relevant non-major bleeding was defined as overt major bleeding that did not meet the criteria for major bleeding but that was associated with need for medical intervention, unscheduled contact with a clinician, interruption or discontinuation of study drug, or impairment of activities of daily living.

In the Hokusai-VTE study\textsuperscript{15}, the incidence of clinically relevant bleeding was statistically significantly lower with edoxaban compared to warfarin (8.5% with edoxaban vs 10.3% with warfarin HR 0.81 95% CI 0.71-0.94 p=0.004 for superiority).

There is currently no specific, established antidote to edoxaban. However data suggest reversibility with prothrombin complex concentrate (PCC)\textsuperscript{16}.

COST\textsuperscript{*}

<table>
<thead>
<tr>
<th></th>
<th>Cost per patient (ex VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 1\textsuperscript{st} month (including LMWH)</td>
<td>£80-140</td>
</tr>
<tr>
<td>Edoxaban after 1\textsuperscript{st} month</td>
<td>£766.50 per year</td>
</tr>
<tr>
<td>Enoxaparin 1.5mg/kg for first 9 days (120mg daily assumed) with dose adjusted warfarin started on day 1 (based on 6mg average daily warfarin dose and 6 INR visits at £20 per visit) for 6 months</td>
<td>£428 per course</td>
</tr>
<tr>
<td>Dose adjusted warfarin (based on 6mg average daily dose and 6-12 INR visits at £20 per visit) Estimated demand would be up to 13 patients per 100,000 adult population at 5 years giving an estimated cost of £10,500 per 100,000 population at 5 years (based on NICE TA 327\textsuperscript{13} (dabigatran) costing template as no costing template was developed for edoxaban).</td>
<td>£144-£264 per year</td>
</tr>
</tbody>
</table>

PATIENT FACTORS\textsuperscript{**}

Patients with 1 or more of: moderate-severe renal impairment (CrCl 15-50ml/min), body weight <60Kg or use of concomitant erythromycin, ciclosporin, dronedarone or ketoconazole should have the dose of edoxaban reduced to 30mg daily.

Duration of therapy with edoxaban for the prevention of recurrent VTE should be individualised following careful assessment of the chance of clinical benefits versus the risk of harm from bleeding. In patients with elevated liver enzymes (ALT/AST>2 x upper limit normal [ULN]) or total bilirubin ≥1.5 x ULN edoxaban should be used with caution. Prior to initiating treatment a liver function test should be performed.

In patients with concomitant conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risk should be made before combining this therapy.

Consult SPC for further details at: www.medicines.org.uk

PRESCRIBING AND IMPLEMENTATION INFORMATION

- Treatment should be started by a specialist in the management of VTE. Following initiation, prescribing can be continued in primary care by the GP. Initial supply of edoxaban should be made by secondary care.
- Duration of treatment must be communicated to the GP on initiation of treatment.
- Patients should receive at least 5 days treatment with a parenteral anticoagulant before starting edoxaban.
- Recommended starting dose of edoxaban for the treatment and prevention of VTE is 60mg daily.
- Renal function should be assessed in all patients before starting edoxaban and at least once a year and more frequently in those with a suspected decline in renal function. Patients with 1 or more of: moderate-severe renal impairment (CrCl 15-50ml/min), body weight <60Kg or use of concomitant erythromycin, ciclosporin, dronedarone or ketoconazole should have the dose of edoxaban reduced to 30mg daily. Edoxaban is not recommended if creatinine clearance is <15ml/min.
- When switching from warfarin to edoxaban, stop warfarin (or other vitamin K antagonist (VKA)) and start edoxaban when the INR is ≤ 2.5.
- When switching from edoxaban to warfarin, start warfarin, reduce edoxaban to 30mg daily and continue until INR ≥ 2.0. (In patients already on edoxaban 30mg daily, reduce the dose to 15mg daily and continue until the INR ≥2.0).
- When switching from parenteral anticoagulant to edoxaban, start edoxaban at the time next scheduled dose of LMWH would be administered or 4 hours after ceasing intravenous heparin. These agents should not be given simultaneously.
- When switching from edoxaban to parenteral anticoagulation, start parenteral therapy at the time next scheduled dose of edoxaban would be administered. These agents should not be given simultaneously.
- A missed dose of edoxaban should be taken immediately and then continued once daily on the following day.
- Patients should be issued with a Patient Alert Card (available from manufacturer or can be downloaded from SPC).
# Rivaroxaban (Xarelto®▼) for the Treatment of Deep Vein Thrombosis and Prevention of Recurrent Deep Vein Thrombosis and Pulmonary Embolism

## EFFECTIVENESS

Rivaroxaban is an anticoagulant that directly inhibits factor Xa. 3449 patients presenting with acute DVT (but no PE) were randomised to either oral rivaroxaban alone (15mg twice daily for 21 days then 20mg daily) or sub-cutaneous enoxaparin (1mg/kg twice daily) followed by a vitamin K antagonist (aiming for an INR 2-3) (EINSTEIN-DVT)\(^{17}\). The primary efficacy outcome was symptomatic, recurrent venous thromboembolism (composite of DVT or non-fatal or fatal PE). Rivaroxaban had non-inferior efficacy with respect to the primary efficacy outcome when compared to LMWH plus vitamin K antagonist - 36 events (2.1%) for rivaroxaban Vs 51 events (3.0%) for LMWH plus vitamin K antagonist, HR 0.68 95% CI 0.44-1.04; p<0.001.

## SAFETY

In the EINSTEIN-DVT\(^{17}\) study, there was no difference in the principal safety outcome (major bleeding or clinically relevant non major bleeding) which occurred in 8.1% of patients in each study group.

Rivaroxaban is contraindicated in patients with a creatinine clearance < 15ml/min. It is not removable by dialysis.

Although there is no specific, established antidote available, preliminary data suggest reversibility with activated prothrombin complex concentrate (PCC)\(^{18}\).

## COST PER PATIENT*

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Cost per patient (ex VAT)</th>
<th>Cost per course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 1st month (15mg twice daily for 21 days then 20mg daily)</td>
<td>£88.20</td>
<td>£428 per course</td>
</tr>
<tr>
<td>Rivaroxaban after 1st month</td>
<td>£657 per year</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin 1.5mg/kg for first 9 days (120mg daily assumed) with dose adjusted warfarin started on day 1 (based on 6mg average daily warfarin dose and 6 INR visits at £20 per visit) for 6 months</td>
<td>£144-£264 per year</td>
<td></td>
</tr>
<tr>
<td>Dose adjusted warfarin (based on 6mg average daily dose and 6-12 INR visits at £20 per visit)</td>
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</tbody>
</table>

Based on the NICE costing template developed for TA 261, estimated demand would be up to 66 per 100,000 population. This gives an estimated cost of £15,576-£53,460 per 100,000 population (dependant on treatment duration). For those patients normally treated with long term LMWH, rivaroxaban would provide significant cost savings along with treatment with a licensed product.

## PATIENT FACTORS\(^{19}\)

- ** Patients with moderate to severe renal impairment (CrCl 15-49 ml/min) should have a dose reduction to 15mg twice daily for 21 days followed by 15mg daily. Rivaroxaban should be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min) due to an increase in plasma concentration of rivaroxaban.
- ** Rivaroxaban is contraindicated in hepatic disease associated with a clinical bleeding risk and in patients taking azole antimycotics (except fluconazole) and HIV protease inhibitors.

Consult SPC for more details at: [www.medicines.org.uk](http://www.medicines.org.uk)

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### PRESCRIBING AND IMPLEMENTATION INFORMATION

- ** Treatment should be started by a specialist in the management of DVT. Following initiation, prescribing can be continued in primary care by the GP. Initial supply of rivaroxaban should be made by secondary care and include the loading dose (first 21 days) and the start of the maintenance dose.
- ** Duration of treatment must be communicated to the GP on initiation of treatment.
- ** The recommended dose of rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE is 15mg bd for 21 days followed by 20mg daily, taken with food. In patients with moderate to severe renal impairment (CrCl 15-49 ml/min) the dose should be reduced to 15mg twice daily for 21 days followed by 15mg daily with food. The effect of rivaroxaban on clotting times is predictable, therefore routine monitoring is not required.
- ** When switching from warfarin to rivaroxaban, stop warfarin and start rivaroxaban when INR $\leq 3.0$.
- ** When switching from rivaroxaban to warfarin, give both agents concurrently until INR $\geq 2.0$ (check INR just before rivaroxaban dose is due).
- ** When switching from parenteral anticoagulant to rivaroxaban, start rivaroxaban 0-2 hours before next dose of LMWH is due or at the same time as the continuous intravenous infusion of unfractionated heparin is stopped.
- ** When switching from rivaroxaban to parenteral anticoagulant, give the first parenteral dose when next dose of rivaroxaban is due.
- ** If a dose is missed during the 15mg twice daily treatment phase (day1-21), the patient should take rivaroxaban immediately to ensure intake of 30mg per day. In this case, two 15mg tablets may be taken at once. The patient should continue with the regular 15mg twice daily on the following day. If a dose is missed during the once daily treatment phase the patient should take the tablet immediately when they realise a dose has been missed and continue on the following day with the usual daily dose.
- ** Patients should be given a rivaroxaban alert card available from the manufacturer.
Rivaroxaban (Xarelto®▼) for the Treatment of PE and Prevention of Recurrent DVT and PE

**EFFECTIVENESS**
Rivaroxaban is an anticoagulant that directly inhibits factor Xa. 4832 patients presenting with acute PE (with or without DVT) were randomised to either oral rivaroxaban alone (15mg twice daily for 21 days then 20mg daily) or sub-cutaneous enoxaparin (1mg/kg twice daily) followed by a vitamin K antagonist (aiming for an INR 2-3) for 3, 6 or 12 months (EINSTEIN-PE)\(^{20}\). The primary efficacy outcome was symptomatic, recurrent venous thromboembolism (composite of DVT or non-fatal or fatal PE). Rivaroxaban had non-inferior efficacy with respect to the primary efficacy outcome when compared to LMWH plus vitamin K antagonist - 50 events (2.1%) for rivaroxaban Vs 44 events (1.8%) for LMWH plus vitamin K antagonist, HR 1.12 95% CI 0.75-1.68 p=0.003.

**SAFETY**
In the EINSTEIN-PE\(^{20}\) study, there was no difference in the principal safety outcome (major bleeding or clinically relevant non major bleeding) which occurred in 10.3% of patients in the Rivaroxaban group and 11.4% in the standard treatment group, HR 0.9, 95% CI 0.76-1.07 p=0.23

Rivaroxaban is contraindicated in patients with a creatinine clearance < 15ml/min. It is not removable by dialysis. Although there is no specific, established antidote available, preliminary data suggest reversibility with activated prothrombin complex concentrate (PCC)\(^{18}\).

**COST PER PATIENT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost per patient (ex VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 1st month (15mg twice daily for 21 days then 20mg daily)</td>
<td>£88.20</td>
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<td>£144-£264 per year</td>
</tr>
</tbody>
</table>

Based on the NICE costing template developed for TA 287\(^{2}\), estimated demand would be up to 41 per 100,000 population. This gives an estimated annual incremental cost of £19,800 per 100,000 population (dependant on treatment duration). For those patients normally treated with long term LMWH, rivaroxaban would provide significant cost savings along with treatment with a licensed product.

**PATIENT FACTORS**
Patients with moderate to severe renal impairment (CrCl 15-49 ml/min) should have a dose reduction to 15mg twice daily for 21 days followed by 15mg daily. Rivaroxaban should be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min) due to an increase in plasma concentration of rivaroxaban.

Rivaroxaban is contraindicated in hepatic disease associated with a clinical bleeding risk and in patients taking azole antifungalics (except fluconazole) and HIV protease inhibitors.

Consult SPC for more details at: [www.medicines.org.uk](http://www.medicines.org.uk)

**PRESCRIBING AND IMPLEMENTATION INFORMATION**
- Treatment should be started by a specialist in the management of PE. Following initiation, prescribing can be continued in primary care by the GP. **Initial supply of rivaroxaban should be made by secondary care and include the loading dose (first 21 days) and the start of the maintenance dose.**
- **Duration of treatment must be communicated to the GP on initiation of treatment.**
- The recommended dose of rivaroxaban for the treatment of PE and prevention of recurrent DVT and PE is 15mg bd for 21 days followed by 20mg daily, taken with food. In patients with moderate to severe renal impairment (CrCl 15-49 ml/min) the dose should be reduced to 15mg twice daily for 21 days followed by 15mg daily with food. Rivaroxaban is contraindicated in patients with a creatinine clearance < 15ml/min. The effect of rivaroxaban on clotting times is predictable, therefore routine monitoring is not required.
- When switching from warfarin to rivaroxaban, stop warfarin and start rivaroxaban when INR ≤3.0.
- When switching from rivaroxaban to warfarin, give both agents concurrently until INR ≥ 2.0 (check INR just before rivaroxaban dose is due).
- When switching from parenteral anticoagulant to rivaroxaban, start rivaroxaban 0-2 hours before next dose of LMWH is due or at the same time as the continuous intravenous infusion of unfractionated heparin is stopped.
- When switching from rivaroxaban to parenteral anticoagulant, give the first parenteral dose when next dose of rivaroxaban is due.
- If a dose is missed during the 15mg twice daily treatment phase (day 1-21), the patient should take rivaroxaban immediately to ensure intake of 30mg per day. In this case, two 15mg tablets may be taken at once. The patient should continue with the regular 15mg twice daily on the following day. If a dose is missed during the once daily treatment phase the patient should take the tablet immediately when they realise a dose has been missed and continue on the following day with the usual daily dose.
- Patients should be given a rivaroxaban alert card available from the manufacturer.
References


