What is dabigatran etexilate?

Dabigatran etexilate is a novel reversible oral direct thrombin inhibitor that provides its anticoagulant effect by specifically and selectively blocking the activity of thrombin (both free and clot bound).\textsuperscript{1,2} Thrombin is the central enzyme in clot (thrombus) formation, responsible for the conversion of fibrinogen to fibrin.

Dabigatran etexilate key characteristics

- Does not require routine coagulation monitoring or dose titration\textsuperscript{3-5}
- Predictable and consistent anticoagulant effect\textsuperscript{5,6}
- Rapid onset / offset of action\textsuperscript{5}
- Low potential for drug-drug interactions\textsuperscript{7-9}
- No food-drug interactions and dosing independent of meals or dietary restrictions\textsuperscript{10}
Dabigatran etexilate

The role of thrombin

Thrombin is an enzyme in the blood that causes blood to clot by facilitating the conversion of the protein fibrinogen to fibrin. Thrombin clips a small piece off the large protein fibrinogen, causing it to assemble into large fibrous networks, converting fibrinogen from a soluble substance into insoluble fibrin. These networks of fibrin strands then trap blood cells, leading to the formation of blood clots or thrombi.

Mechanism of Action

- All anticoagulants work by directly or indirectly inhibiting thrombin which plays a key role in thrombus formation.1,11,12
- Unlike other anticoagulants, the effects of direct thrombin inhibitors such as dabigatran etexilate are limited to thrombin.1,13

Dabigatran etexilate works by:

- specifically and selectively binding to thrombin, thereby blocking its activity.13
- blocking both free and clot-bound thrombin, providing more effective thrombin inhibition than heparins (which block mainly free thrombin).1,2
- binding with existing thrombin, the starting point for up-regulation of the clotting factors which are responsible for additional thrombin production.1,2,13
- interfering with thrombin and its effects on the coagulation cascade, e.g.:1,13
  - conversion of fibrinogen to fibrin by thrombin
  - platelet activation by thrombin (thrombin is the most potent stimulus for platelet activation)1
  - activation of clotting Factors V, VIII and XI by thrombin (even small amounts of thrombin can initiate the up-regulation of these clotting factors).1,13

Efficacy and safety

Prevention of venous thromboembolism (VTE) in patients following total knee or hip replacement

- Dabigatran etexilate provides VTE prevention comparable to enoxaparin after total knee or hip replacement.16
- Results from the RE-NOVATE™, RENOVATE™ and RE-MODEL™ trials showed that dabigatran etexilate was as effective as enoxaparin at preventing VTE and all-cause mortality.16
- Dabigatran etexilate’s safety profile is comparable to enoxaparin after total knee or hip replacement.16
- Low incidence of major bleeding events, similar to enoxaparin.16

Background information – For medical media outside the US only

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Key indications under investigation

The extensive RE-VOLUTION® clinical trial programme is evaluating the efficacy and safety of dabigatran etexilate against current standard therapies in five major therapeutic areas in over 38,000 patients globally.

<table>
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<tr>
<th>RE-VOLUTION® trials</th>
<th>Indication under investigation</th>
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<tr>
<td>RE-NOVATE®</td>
<td>Primary prevention of VTE following hip replacement surgery</td>
<td>Completed and published17</td>
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<tr>
<td>RE-LY®</td>
<td>Prevention of stroke in patients with non-valvular AF</td>
<td>Completed. Results published in the New England Journal of Medicine, 200920,21</td>
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<tr>
<td>RE-COVER® &amp; RECOVER™ II</td>
<td>Treatment of acute VTE</td>
<td>Completed and published22 Ongoing</td>
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<td>RE-DEEM™</td>
<td>Secondary prevention of cardiac events in patients with acute coronary syndrome</td>
<td>Completed</td>
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Current licensed indication

Based on the results of RE-NOVATE® and RE-MODEL™,13,14 dabigatran etexilate has already been approved in 75 countries for the primary prevention of blood clots (venous thromboembolic events) in adults who have undergone elective total hip or elective total knee replacement surgery.4

The registration process for dabigatran etexilate in the indication of prevention of stroke and systemic embolism in patients with atrial fibrillation is underway in the US, Europe, Canada, Australia, Japan and additional countries. The FDA has granted priority review designation for dabigatran etexilate. Boehringer Ingelheim expects to launch dabigatran etexilate for the prevention of stroke and systemic embolisms in AF in first countries by end of 2010 or beginning of 2011.

Disclaimer

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation prevention. This information is provided for medical education purposes only.

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References


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