Rivaroxaban for the treatment of deep vein thrombosis or pulmonary embolism

Rivaroxaban is a new oral anticoagulant indicated for the treatment of venous thromboembolic events (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). Rivaroxaban inhibits Factor-Xa in the coagulation cascade.

Dosage

The recommended dose of rivaroxaban for patients initiating DVT or PE treatment is 15 mg twice daily for 3 weeks, followed by 20 mg once daily.

PharmaCare Coverage

PharmaCare coverage of rivaroxaban (15 mg and 20 mg tablets) for the treatment of DVT or PE is available as an alternative to therapy with warfarin (bridged concurrently with a heparin product on a short-term basis until International Normalized Ratio [INR] is within the therapeutic range). Coverage for rivaroxaban is provided for up to 6 months. See the coverage criteria.

EINSTEIN-DVT and EINSTEIN-PE: rivaroxaban's pivotal clinical trials for the treatment of acute, symptomatic DVT and PE with or without DVT

EINSTEIN-DVT and EINSTEIN-PE are open-label, randomized non-inferiority studies that evaluated the efficacy and safety of rivaroxaban in patients with acute, symptomatic, proximal DVT without symptomatic PE, and in patients with symptomatic PE with or without DVT, respectively. In the trials, patients were randomized to receive either oral rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or standard therapy for 3, 6 or 12 months.[1,2] Patients receiving standard therapy received a vitamin K antagonist (either warfarin or acenocoumarol, dose-adjusted to an INR of 2.0 to 3.0) A short-term course of subcutaneous enoxaparin (1 mg/kg twice daily) overlapped with the initiation of warfarin for bridging; that is, enoxaparin was discontinued when the INR was 2.0 or greater for 2 consecutive days and at least 5 days of enoxaparin had been given. The treatment duration was determined by the investigator at the time of randomization based on local risk assessment and treatment guidelines. Although the use of nonsteroidal anti-inflammatory and anti-platelet agents were discouraged in the trial, aspirin (up to 100 mg daily), clopidogrel (75 mg daily), or both, were allowed if indicated.[1,2]

Efficacy

For the primary efficacy outcome of symptomatic, recurrent venous thromboembolism (VTE), defined as the composite of DVT, non-fatal PE, or fatal PE. In both trials, rivaroxaban was non-inferior to standard therapy of enoxaparin plus a vitamin K antagonist (hazard ratio 0.68; 95% CI, 0.44 to 1.04; $p<0.001$ for non-inferiority in the DVT trial; and hazard ratio 1.12; 95%CI, 0.75 to 1.68; $p=0.003$ in PE trial).[1,2]

In EINSTEIN-DVT and EINSTEIN-PE, few patients with active cancer (6% and 4.7% of participants respectively) were included in the study; as such, these results may not be generalizable to patients with active cancer.[1,2]

Safety

For the primary safety outcome of clinically relevant bleeding, defined as the composite measure of major or clinically relevant non-major bleeding, rivaroxaban was similar to standard therapy with enoxaparin plus a vitamin K antagonist.

Note that at present, there is no established effective antidote for rivaroxaban. There is limited experience with using procoagulants to manage bleeding secondary to rivaroxaban.[4] Rivaroxaban should only be prescribed for patients who have ready access to appropriate medical services to manage a major bleeding event. Cautious use of rivaroxaban is recommended until greater clinical experience is available.

Patients with renal impairment have higher risk of bleeding with rivaroxaban. Therefore, it is important to monitor renal function regularly. Patients with a CrCl<30ml/min were excluded from these trials.[1,2] Other factors that increase bleeding risk should also be assessed and monitored (see product monograph).

Duration of Anticoagulation

In general, there is a lack of definitive information about the optimal duration of treatment for acute DVT or PE with any anticoagulant (warfarin, a heparin product, or a new oral anticoagulant). Clinical trials and guidelines have reviewed anticoagulation for less than 3 months, and extended therapy beyond 3 months. To date, there is limited data regarding the efficacy and safety of extended therapy with rivaroxaban for the treatment of DVT or PE.

In EINSTEIN-DVT and EINSTEIN-PE, only 55% and 57% of all patients completed a 6-month course of treatment, respectively.[1,2] Of the DVT patient subgroup initially allocated to receive 12 months of anticoagulation with rivaroxaban, only 10% completed the full 12 months of therapy.[1] There is no data comparing rivaroxaban to standard therapy beyond 12 months.[1,2] The duration of anticoagulation with warfarin, a heparin product, or rivaroxaban is a clinical decision that requires individualized evaluation of the patient's risks and benefits of therapy.

Cost-Effectiveness Dependent on Duration

Based on the pharmacoeconomic analysis by the Canadian Agency for Drugs and Technologies in Health (CADTH), rivaroxaban appeared to be cost saving (compared to enoxaparin plus warfarin) when treating patients for 3 months, and likely cost neutral when treating patients for 6 months. However, when used for longer than 6 months, rivaroxaban is more costly than heparin plus warfarin.[6,7] As such, patients with an intended duration of therapy longer than 6 months should be considered for initiation on heparin/warfarin.

Current Guidelines on Duration of Anticoagulation

When CADTH reviewed DVT treatment guidelines, no evidence-based Canadian practice guidelines were identified.[5]

In 2012, the American College of Chest Physicians (ACCP) published clinical practice guidelines with the following recommendations regarding duration of anticoagulation treatment in acute DVT.[4]

Suggested duration of anticoagulation treatment per ACCP clinical practice guidelines

Nature of Acute VTE and PE		Duration of Anticoagulation
Provoked DVT	DVT (proximal or isolated distal) of the leg provoked by surgery	3 months
	DVT (proximal or isolated distal) of the leg provoked by a nonsurgical transient risk factor	3 months
Unprovoked DVT*	First VTE event • proximal DVT of the leg • **low or moderate** bleeding risk^	Extended therapy§
	First VTE event • proximal DVT of the leg • **high** bleeding risk^	3 months
	First VTE event • isolated distal DVT of the leg	3 months
	Second unprovoked VTE event • **low to moderate** bleeding risk^	Extended therapy§
	Second unprovoked VTE event • **high** bleeding risk^	3 months
Provoked PE	PE provoked by surgery	3 months
	PE provoked by a non-surgical transient factor	3 months
Unprovoked PE	First VTE event • **low to moderate** bleeding risk^	Extended therapy§
	First VTE event • **high** bleeding risk^	3 months
	Second VTE event • **low to moderate** bleeding risk^	Extended therapy§
	Second VTE event • **high** bleeding risk^	3 months

Footnotes:
*The ACCP recommends treatment with anticoagulation for at least 3 months in patients with an unprovoked DVT of the leg (isolated distal or proximal); after 3 months of treatment, evaluate the risk-benefit ratio of extended therapy.
^ACCP defines low bleeding risk as zero risk factors for bleeding, moderate risk as 1 risk factor, and high risk as ≥2 risk factors. Examples of risk factors include age>65 years, previous bleeding, renal failure, liver failure, diabetes, and numerous others. Refer to Table 2 of the ACCP Guidelines for a more complete listing of risk factors.[3]
§The ACCP defines extended therapy as anticoagulation that is continued beyond 3 months without a scheduled stop date. ACCP recommends periodic reassessment of continued anticoagulation in all patients who receive extended therapy.

Prescribers should carefully consider patient-specific risks and benefits, the intended duration of therapy, costs, and patient preferences in the selection of an anticoagulation agent. In patients whom extended therapy is required, the ACCP suggests continued treatment with the same anticoagulant used in the first 3 months of therapy.[4]

References

1. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363;26:2499-510.
2. EINSTEIN Investigators. Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97
3. Health Canada Drug Product Database Product Monograph rivaroxaban. Ottawa, ON: Health Canada; 2013 [cited 2013 May 28]. Available from: webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
4. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Th erapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence -Based Clinical Practice Guidelines. Chest . 2012 Feb;141(2 Suppl):e419S-e494S.
5. Canadian Agency for Drugs and Technologies in Health. Rivaroxaban for the treatment of deep vein thrombosis: a review of the guidelines [Internet]. Ottawa: CADTH; 2012 Dec 4. [cited 2013 May 28]. Available from: www.cadth.ca/media/pdf/htis/jan-2013/RC0411%20rivaroxaban%20for%20DVT%20Final.pdf
6. CDEC final recommendation: rivaroxaban (Xarelto – Bayer Inc.) New indication: deep vein thrombosis (treatment) without symptomatic pulmonary embolism [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012 Aug 16. [cited 2013 May 28]. Available from: www.cadth.ca/media/cdr/complete/cdr_complete_Xarelto%20DVT_Aug-20-12_e.pdf
7. CDEC final recommendation: rivaroxaban (Xarelto – Bayer Inc.) New indication: pulmonary embolism [Internet]: Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014 Mar 26. [cited 2014 Sep 17]. Available from: www.cadth.ca/media/cdr/complete/SR0327_complete_Xarelto%20PEm_Mar-28-14.pdf