VTE
(Venous thromboembolism)[7]

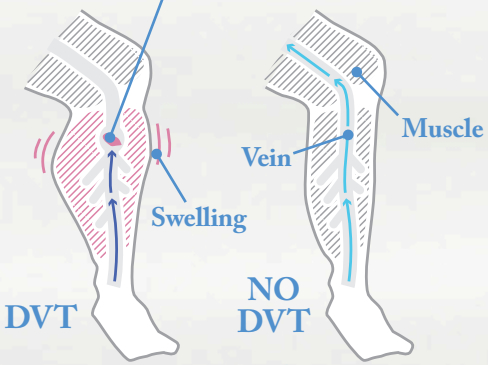
3rd most common cardiovascular condition worldwide[1]

Most common avoidable cause of hospital death[2]

EVERY 37 SECONDS **someone in the Western world dies from a blood clot**[3,4]

Deep vein thrombosis (DVT)

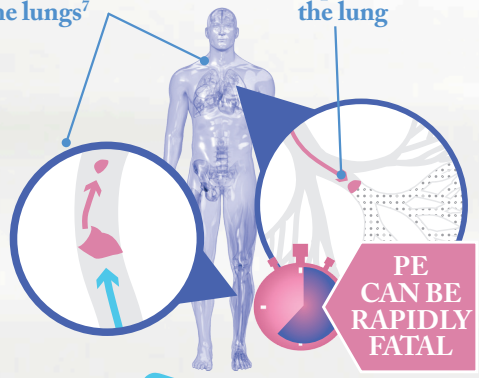
Blood clot forms in a deep vein – most often in the leg[7]



Pulmonary embolism (PE)

Part of blood clot breaks off and travels to the lungs[7]

Clot blocks blood supply to part of the lung

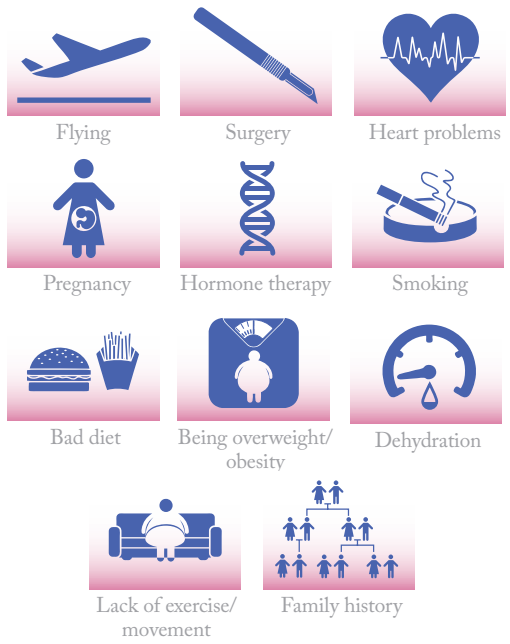


Symptoms

Symptoms of DVT[6,8]
- ✓ Pain
- ✓ Swelling
- ✓ Redness of the area
- ✓ Dilation of the surface veins
- ✓ Skin warm to touch

Symptoms of PE[5,8]
- ✓ Shortness of breath
- ✓ Chest pain
- ✓ Rapid heart rate
- ✓ Coughing blood
- ✓ Light headedness

Know the Risk Factors[6,8]



It is important doctors inform patients of the risk factors as well as the signs and symptoms, so people can seek appropriate medical attention for the treatment and prevention of VTE

REFERENCES: **1)** Naess IA,Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692-699 **2)** Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133,(6 Suppl)381S-453S **3)** Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98,(4)756-764 **4)** Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2-e220 **5)** Mayo Clinic. Deep vein thrombosis. Available at: http://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/basics/ symptoms/con-20031922. Accessed June 2014 **6)** Turpie AGG, Chin BSP, Lip GYH. Venous thromboembolism: pathophysiology, clinical features, and prevention. BMJ 2002;325:887–890 **7)** Patient UK. Deep vein thrombosis. Available at: http://www.patient.co.uk/health/Deep-Vein-Thrombosis.htm Accessed June 2014 **8)** NHS Choices. Causes of deep vein thrombosis (DVT). Available at: http://www.nhs.uk/Conditions/Deep-vein-thrombosis/Pages/Causes.aspx. Accessed June 2014

The Development of Anticoagulants

1930s

Heparin (unfractioned)[1]

✓ Effective (as used according to prescriber information)

Injection

1940s

Vitamin K Antagonists (VKAs) e.g. warfarin[1]

✓ Effective (if INR is in therapeutic range)

✓ Oral administration

Regular coagulation monitoring

Dose adjustment

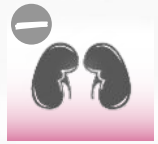
Many food and drug interactions

1980s

Low Molecular Weight Heparins (LMWHs) e.g. enoxaparin[2]

✓ Effective (as used according to prescriber information)

Injection



Can accumulate in patients with kidney impairment

What Do Anticoagulants Do?

Anticoagulants are one of the first lines of defence against **blood clots**

*Venous thromboembolism (VTE)

2000s

Novel Oral Anticoagulants (OACs)

- Direct Factor Xa Inhibitors (Xabans) e.g. rivaroxaban, apixaban and edoxaban[3]
- Direct Thrombin Inhibitors (DTIs) e.g. dabigatran[4]

1st Xaban Approved 2008

Rivaroxaban

Now approved in 5 indications and its ongoing investigation will include more than 275,000 patients in both clinical trial and real world settings[6]

Xabans can overcome the limitations of older anticoagulants to prevent and/or treat venous and arterial thromboembolic (VAT) conditions[5]

Oral administration

Rapid onset of action

Predictable anticoagulation without need for routine monitoring or dose adjustment

Low risk of drug-drug interactions

No significant food interactions

It is important doctors and patients discuss the benefits and risks of the different anticoagulants to help identify the best treatment for optimal protection that is suited to maintain their quality of life

REFERENCES: **1)** Ansell J, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004. 126 (3 Suppl): 204S-233S **2)** Hirsh J, Anand SS, Halperin JL, et al. Guide to anticoagulant therapy: Heparin : a statement for healthcare professionals from the American Heart Association. Circulation. 2001;103,(24)2994-3018 **3)** Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors Rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. Clin Pharmacokinet. 2013; 52(4) 243-54 **4)** Lee CJ, Ansell JE. Direct thrombin inhibitors, BJCP. 2011. 72(4) 581-592 **5)** Cohen AT, Imfeld S, et al. Phase III Trials of New Oral Anticoagulants in the Acute Treatment and Secondary Prevention of VTE: Comparison and Critique of Study Methodology and Results. Adv Ther (2014) 31:473–493 **6)** Xarelto [SmPC]. Berlin, Germany: Bayer Pharma AG; November 2013

About Rivaroxaban

What is Rivaroxaban?

Rivaroxaban is the first direct oral Factor Xa Inhibitor developed to prevent and treat dangerous blood clots, with the potential to improve clinical outcomes and quality of life for a broad range of patients with, or at risk of venous and arterial thromboembolism (VAT).

Benefits of Rivaroxaban include[1]:

- Oral administration
- Rapid onset of action
- Predictable anticoagulation without need for routine coagulation monitoring or dose adjustment
- Low risk of drug-drug interactions
- No significant food interactions

Rivaroxaban is approved for five indications in eight distinct areas of use, protecting patients from blood clots across more VAT conditions than any other novel OAC[1]

VTE Prevention in Adult Patients Following Elective Hip or Knee Replacement:

For adult patients who have had hip or knee replacement, one 10 mg tablet, once-daily rivaroxaban provides superior protection against venous thromboembolism (VTE) with similar safety compared to the low molecular weight heparin (LMWH) enoxaparin[2]. Patients on rivaroxaban also experience fewer symptomatic VTEs and simliar rates of major bleeding complications post-surgery compared to conventional treatments[3].

Stroke Prevention in Patients with Non-Valvular AF:

For adult patients with non-valvular atrial fibrillation (AF), once-daily rivaroxaban provides effective stroke prevention without the need for routine coagulation monitoring[1,4]. Importantly, rivaroxaban can prevent stroke without increasing the risk of heart attack and lowers the rate of the most feared intracranial and fatal bleeds, compared with warfarin while demonstrating a reassuring bleeding profile with similar overall bleeding rates[1,5]. Major gastrointestinal (GI) bleeds were more common with rivaroxaban than warfarin[5]. It is also the only novel OAC with a specific and effective dose evaluated for patients with renal impairment.

DVT Treatment and Prevention:

For adult patients with deep vein thrombosis (DVT), rivaroxaban is the first novel OAC globally approved for acute treatment and the prevention of recurrent VTE. As the oral, single-drug approach, rivaroxaban is effective in providing simplified patient management from hospital to home without the need for injections or routine coagulation monitoring[1,6,7,8]. Additionally, rivaroxaban has a similar low rate of major bleeding compared with the dual-drug approach of LMWH and vitamin K antagonists (VKA)[6].

PE Treatment and Prevention:

For adult patients with pulmonary embolism (PE), rivaroxaban is the first novel OAC globally approved for acute treatment and the prevention of recurrent VTE. As the oral, single-drug approach, rivaroxaban is effective in protecting against life-threatening PEs without the need for injections or routine coagulation monitoring[6], providing simplified patient management from hospital to home. Additionally, rivaroxaban significantly lowers the risk of major bleeding compared with the dual-drug approach of LMWH and VKA[7].

Prevention of Atherothrombotic Events after an ACS in Patients with Elevated Cardiac Biomarkers:

For patients with acute coronary syndrome (ACS), rivaroxaban 2.5 mg twice daily in combination with standard antiplatelet therapy* can help reduce atherothrombotic events (CV death, heart attack and stroke) by providing more complete long-term protection than antiplatelet therapy alone. Rates of major bleeding not associated with coronary artery bypass graft (CABG) surgery and intracranial haemorrhage (ICH) were low overall, yet increased with the addition of rivaroxaban. But importantly, there were no increase observed with rivaroxaban in the risk of fatal ICH or fatal bleeding[9,10].

How Does Rivaroxaban Work?

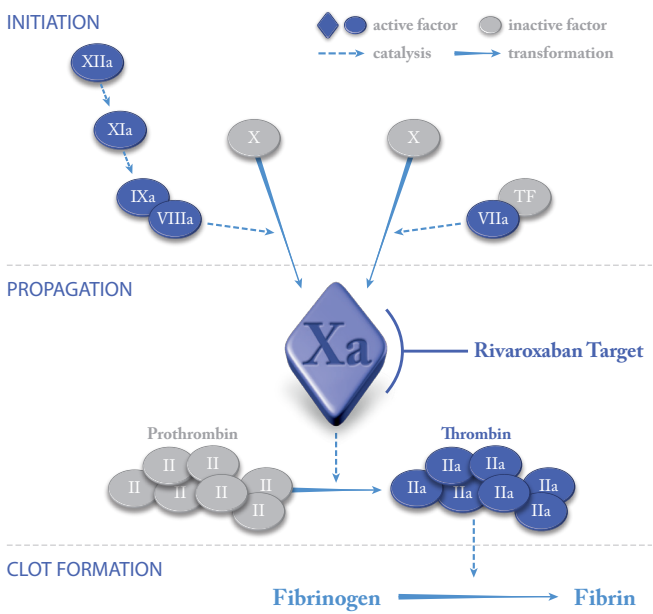
Rivaroxaban is an oral direct Factor Xa Inhibitor, protecting patients against blood clots by selectively targeting Factor Xa, an enzyme which acts at a key point in the blood-clotting (coagulation) process.

Coagulation requires a complex series of chemical reactions and body signals. This process of chemical reactions is often referred to as the 'Clotting Cascade'.

One of the many clotting factors (blood clot proteins) is Factor Xa that is needed to produce thrombin, which promotes the formation of blood clots. One molecule of Factor Xa catalyses the formation of approximately 1,000 thrombin molecules via what is known as a 'thrombin burst'[11,12].

Directly targeting and inhibiting Factor Xa prevents the thrombin burst, rivaroxaban inhibits thrombin generation rather than inhibiting the action of thrombin itself.

Targeting Factor Xa to Inhibit Thrombin Generation



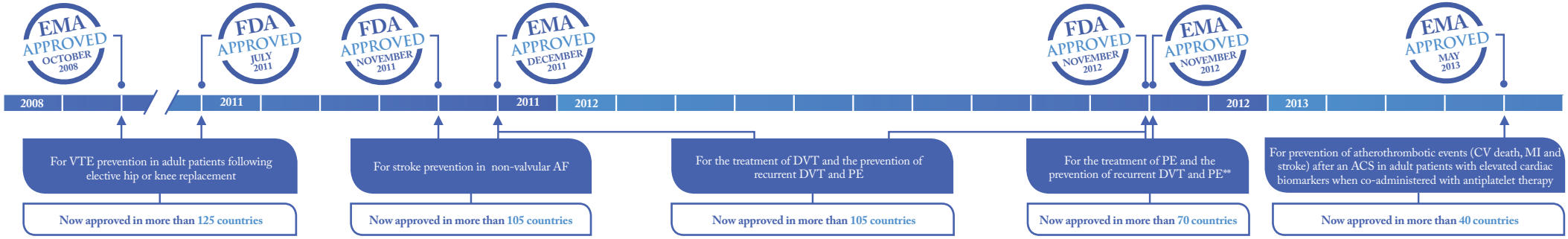
About Rivaroxaban continued...

Rivaroxaban has demonstrated clinical benefit in comparison to older therapy in a broad range of acute and chronic blood-clotting conditions

The Clinical Investigation of Rivaroxaban

- Ten completed Phase III pivotal trials have successfully met or exceeded their primary endpoints, in preventing and/or treating VAT conditions, which has resulted in the approval of rivaroxaban in 5 indications
- The extensive evaluation of rivaroxaban to protect different patient populations at risk of VAT, makes it the most studied novel OAC in the world and will include more than 275,000 patients in both clinical trials and real world settings.

Rivaroxaban Regulatory Milestones



Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name 'Xarelto®'. Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Rivaroxaban is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Rivaroxaban Dosing

Prevention of Stroke and Systemic Embolism
in adults with non-valvular atrial fibrillation with one or more risk factors[a]

- **20 mg OD** — Patients with CrCl > 49 mL/min with food
- **OR**
- **15 mg OD** — Patients with CrCl 15 to 49 mL/min* with food

Treatment of DVT and PE…
…and extended treatment for prevention of recurrent DVT and PE in adults**

- **15 mg BID** — Patients with CrCl > 15 mL/min* with food

AFTER 3 WEEKS TRANSITION TO

- **20 mg OD** — Patients with CrCl > 15 mL/min* with food

Prevention of VTE in adults undergoing elective hip or knee replacement

- **10 mg OD** — Patients with CrCl > 15 mL/min*

The initial dose should be taken 6 to 10 hours after surgery once haemostasis has been established

Secondary prevention in ACS in combination with standard antiplatelet therapy[b]
in adults with elevated cardiac biomarkers[c]

- **2.5 mg BID** — Patients with CrCl > 15 mL/min*

The initial dose should be taken after stabilization of the ACS event

[a]Such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack; [b]ASA alone or in combination with a thienopyridine (clopidogrel or ticlopidine); [c]Troponin-I/T; creatine kinase-muscle and brain isoenzyme (CK-MB)
*Not indicated in patients with CrCl < 15 ml/min; use with caution in patients with CrCl 15-29 ml/min; **Rivaroxaban is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present hemodynamic instability or who may recieve thrombolysis or pulmonary embolectomy

To learn more, please visit https://prescribe.xarelto.com
To learn more about thrombosis, please visit www.thrombosisadviser.com
To learn more about VAT, please visit www.VATspace.com
To learn more about 'Xarelto', please visit www.xarelto.com

References

1) Xarelto [summary of product characteristics]. Berlin, Germany: Bayer Pharma AG; November 2013 **2)**Eriksson BI, Kakkar AK, Turpie AG, et al. R1-3 pooled; *J Bone Joint Surg Br.* 2009;91:636–44 **3)** Turpie AG, Haas S, Kreutz R, et al. XAMOS; *Thrombosis and Haemostasis* 2014 Jan; 111(1): 94-102 **4)** Coleman CI, Roberts MS, Sobieraj DM, et al. Effect of dosing frequency on chronic cardiovascular disease medication adherence. *Curr Med Res Opin*. 2012 May;28(5):669-80 **5)** Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF; *N Engl J Med.* 2011; 365:883–891 **6)** The EINSTEIN Investigators. *N Engl J Med.* 2010; 363:2499–2510 **7)** The EINSTEIN–PE Investigators. *N Engl J Med.* 2012; 366:1287-1297 **8)** Kubitza D et al. *J Thromb Haemost* 2005; 3 (Suppl.1): Abstract P1704/Figure1a **9)** Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2011; 32:2999-3054 **10)** Mega JL, Braunwald E, Wiviott SD, et al. ATLAS TIMI 51;*N Engl J Med.* 2012; 366:9-19/pp.14-15 **11)** Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler Thromb Vasc Biol*. 2007; 27(6):1238-1247 **12)** Mann KG, Brummel K, & Butenas S. What is all that thrombin for? *J Thromb Haemost*. 2003; 1(7):1504-151

Rivaroxaban in Venous Thromboembolism (VTE)

Venous Thromboembolism (VTE)

Venous thromboembolism (VTE) is the most common, avoidable cause of hospital death[1].

- The worldwide incidence of VTE is 1 per 1000[2]
- In the EU, more than twice as many people die from VTE than from breast cancer, prostate cancer, AIDS and traffic accidents combined[3]

VTE encompasses two serious conditions:

Deep vein thrombosis (DVT) is a blood clot that forms in the veins that lie deep within the muscles, usually in the leg or pelvis. If all or part of the DVT breaks off and the blood clot moves to block a vessel in the lungs, it is known as a **pulmonary embolism (PE)**[6], which can be rapidly fatal.

Deep vein thrombosis (DVT)

- Even in the absence of a PE, DVT alone can have burdensome and costly consequences such as post-thrombotic syndrome[7]
- The rate of VTE recurrence remains high, with hospital readmission for DVT at 19%[8]

Pulmonary embolism (PE)

- About 1 in 10 deaths that occur in the hospital is caused by pulmonary emboli[11]
- 10–25% of PEs are rapidly fatal[7,12], usually within 2 hours of the onset of symptoms[13]. PE can reoccur, and if it does, it is usually fatal[14]

VTE can be difficult to diagnose, so it is important people are aware of the signs and symptoms

Symptoms of DVT include:
Pain, swelling, redness of the area usually the leg, and dilation of the surface veins; the skin may also be warm to the touch

Symptoms of PE include:
Acute shortness of breath, chest pain, and rapid heart rate; some people may also cough blood

Who is at Risk of VTE?

- Patients undergoing major orthopaedic surgery for hip or knee replacement or major surgery for cancer
  - Without preventative treatment, the absolute DVT risk after hip or knee surgery is between 40% and 60%[1]
- Patient-related, predisposing risk factors include inherited thrombophilia, advanced age, obesity, prior VTE and varicose veins[1]
- Patients admitted to hospital for an acute medical condition

Economic Burden

The complications associated with VTE and its treatment are frequent and costly. The main drivers of these VTE costs are initial and recurrent events requiring hospitalisation.

- In Europe, the annual cost of managing all-cause VTE has been estimated at approximately €4,000 per patient[15]

€3.1bn[9]
= estimated total annual cost for VTE associated care in Europe

VTE Prevention and Treatment

Anticoagulants are the cornerstone of therapy for prevention and treatment of potentially deadly blood clots, but widely used older therapies are associated with significant drawbacks for the patient that challenge optimal treatment.

- The older therapy for **prevention of VTE** associated with orthopaedic surgery is a class of injectable anticoagulant drugs known as low molecular weight heparins (LMWH)
- The older therapy for **treatment of VTE and long-term prevention** is the complex dual-drug approach of daily injections of LMWH followed by a transition to long-term oral therapy with a vitamin K antagonist (VKA), such as warfarin. As well as the difficulties associated with LMWH, managing patients on VKAs such as warfarin can also be challenging

Limitations of older VTE therapies may contribute to their under-utilisation[16], creating challenges for patients and leaving them at risk.

Novel oral anticoagulants (OACs) can overcome the limitations of older anticoagulants to prevent and/or treat venous and arterial thromboembolic (VAT) conditions.

Benefits of novel OACs include[17]:

- Predictable anticoagulation without the need for routine coagulation monitoring or frequent dose adjustment
- Low risk of drug-drug interactions
- No significant food interactions

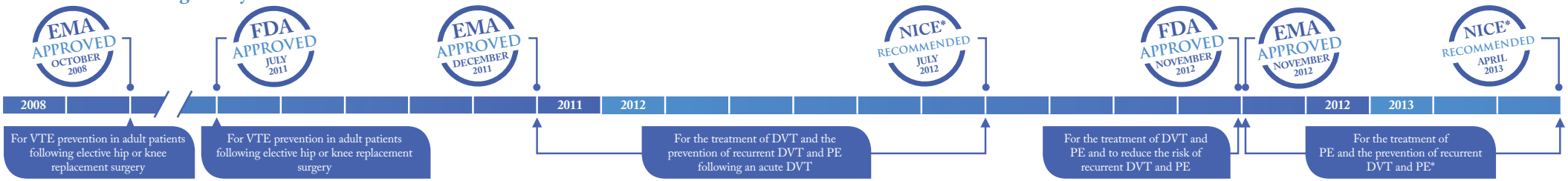
VTE Treatment andPrevention of Recurrence': For adult patients with DVT and PE, rivaroxaban was the first novel OAC globally approved for acute treatment and the prevention of recurrent VTE.

- **DVT:** As the oral, single-drug approach, rivaroxaban is effective in providing simplified patient management from hospital to home without the need for injections or routine coagulation monitoring[17,18,19]. Additionally rivaroxaban has a similar low rate of major bleeding compared with the dual-drug approach of LMWH and VKA[18].
- **PE:** As the oral, single-drug approach, rivaroxaban is effective in protecting against life-threatening PEs[20,21] without the need for injections or routine coagulation monitoring[17,18]. Additionally rivaroxaban significantly lowers the risk of major bleeding compared with the dual-drug approach of LMWH and VKA[20,21].

VTE Prevention in Adult Patients Following Elective Hip or Knee Replacement Surgery: For adult patients who have had major orthopaedic surgery, one 10 mg tablet of rivaroxaban, once-daily provides superior protection against VTE with similar safety compared to the LMWH enoxaparin[17,22,23,24]. Patients on rivaroxaban also experience fewer symptomatic VTEs and similar rates of major bleeding complications post-surgery compared to conventional treatments[25].

Rivaroxaban in Venous Thromboembolism (VTE) continued...

Rivaroxaban VTE Regulatory Milestones



*UK's NICE issued Final Guidance in July 2012 recommending rivaroxaban for National Health Service (NHS) use for the treatment of DVT and the prevention of recurrent DVT and PE following an acute DVT in adults. In April 2013 NICE also issued Final Guidance recommending rivaroxaban for NHS use for the treatment of PE and the prevention of recurrent DVT and PE. The positive NICE appraisals were based on detailed analysis of the clinical and cost-effectiveness benefits of rivaroxaban[19,26]

About Rivaroxaban

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. Rivaroxaban is approved for five indications across eight distinct areas of use, protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other novel OAC:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors
- The treatment of deep vein thrombosis (DVT) in adults
- The treatment of pulmonary embolism (PE) in adults*
- The prevention of recurrent DVT in adults
- The prevention of recurrent PE in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of VTE in adult patients undergoing elective knee replacement surgery
- The prevention of atherothrombotic events (cardiovascular death, heart attack or stroke) after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine

Whilst licences may differ from country to country, across all indications rivaroxaban is approved in more than 125 countries.

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Rivaroxaban is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of rivaroxaban is a very high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a 'Xarelto' Patient Card for patients to support best practice.

To learn more, please visit https://prescribe.xarelto.com
To learn more about thrombosis, please visit www.thrombosisadviser.com
To learn more about VAT, please visit www.VATspace.com
To learn more about 'Xarelto', please visit www.xarelto.com

References:
1) Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133,(6 Suppl)381S-453S **2)** Bramlage P, Pittrow D, & Kirch W. Current concepts for the prevention of venous thromboembolism. *Eur J Clin Invest*. 2005;35 Suppl 1,4-11 **3)** Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost*. 2007;98,(4)756-764 **4)** Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2-e220 **5)** Turpie AG. Thromboprophylaxis After Major Orthopaedic Surgery: State of the Art. *European Instructional Lectures*. 2009;9,29-38 **6)** Patient UK. Deep vein thrombosis. Available at: http://www.patient.co.uk/health/Deep-Vein-Thrombosis.htm Accessed August 2014 **7)** Kearon C. Natural history of venous thromboembolism. *Circulation*. 2003;107,(23 Suppl 1)I22-I30 **8)** Woodward T, Kachroo S, Bookhar BK, et al. Systematic review of the economic burden of venous thromboembolism treatment. Paper presented at ISPOR 15th Annual International Meeting; May 2010; Atlanta, GA. Abstract PCV60 **9)** Coalition to Prevent VTE. Venous thromboembolism: prevention and treatment backgrounder. Available at: http://www.coalitiontopreventvte.org/INDEX_CFM/T/THE_BURDEN_OF_VTE/VID/DCD0A03F_1422_16B3_78E0B9EB0571.HTM Accessed August 2014 **10)** Goldhaber SZ & Morrison RB. Cardiology patient pages. Pulmonary embolism and deep vein thrombosis. *Circulation*. 2002;106,(12)1436-1438 **11)** Geerts WH, Pineo GF, Bergqvist D et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004: 126(3 Suppl): 338S-400S **12)** Heit JA. The epidemiology of venous thromboembolism in the community: Implications for prevention and management. *J Thromb Thrombolysis*. 2006;21,(1)23-29 **13)** Anderson F, Audet AM. Preventing Deep Vein Thrombosis and Pulmonary Embolism: A Practical Guide to Evaluation and Improvement. Center for Outcomes Research, UMass Medical School. 1998. Available at: http://www.outcomes-umassmed.org/DVT/best_practice/ Accessed August 2014 **14)** Nijkeuter M, Söhne M, Tick L et al. The Natural Course of Hemodynamically Stable Pulmonary Embolism. Clinical Outcome and Risk Factors in a Large Prospective Cohort Study. *Chest*. 2007; 131(2) 517-523 **15)** Haas S & Lassen MR. Venous thromboembolism after elective hip and knee replacement surgery. *European Journal of Hospital Pharmacy Practice*. 2010;16, **16)** Lip GY & Lim HS. Atrial fibrillation and stroke prevention. *Lancet Neurol*. 2007;6,(11)981-993 **17)** Xarelto [summary of product characteristics]. Berlin, Germany: Bayer Pharma AG; November 2013 **18)** The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510 **19)** National Institute for Health and Clinical Excellence (NICE). Final appraisal determination. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. Available at http://publications.nice.org.uk/rivaroxaban-for-the-treatment-of-deep-vein-thrombosis-and-prevention-of-recurrent-deep-vein-ta261 Accessed August 2014 **20)** The EINSTEIN–PE Investigators. *N Engl J Med* 2012; 366:1287-1297 **21)** Kubitza D, Becka M, Voith B, et al. Effect of enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939 - an oral, direct Factor Xa inhibitor. *J Thromb Haemost*. 2005; 3 (Suppl 1): Abstract P1704 **22)** Eriksson BI, Borris LC, Friedman RJ et al. RECORD1. *N Engl J Med*. 2008; 358: 2765-2775 **23)** Kakkar AK, Brenner B, Dahl OE et al. RECORD2. *Lancet*. 2008: 372:31-9 **24)** Lassen MR, Ageno W, Borris LC et al. RECORD3. *N Engl J Med*. 2008; 358:2766-2786 **25)** Turpie AG, Haas S, Kreutz R, et al. XAMOS; *Thrombosis and Haemostasis* 2014 Jan; 111(1): 94-102 **26)** National Institute for Health and Clinical Excellence (NICE). Final appraisal determination. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. Available at http://www.nice.org.uk/guidance/TA287/chapter/1-Guidance Accessed August 2014; *Rivaroxaban is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present hemodynamic instability or who may recieve thrombolysis or pulmonary embolectomy