Bayer submits application to EMA for use of rivaroxaban in children with venous thromboembolism

- Adding treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children from birth to 17 years of age with confirmed VTE, including cerebral vein and sinus thrombosis
- Submission based on results from phase 3 EINSTEIN-Jr. study showing convincing efficacy and safety profile for rivaroxaban in children with VTE
- An oral liquid formulation of rivaroxaban that does not require injections and regular monitoring was developed to facilitate pediatric administration
- Patent extension in Europe of six months will be applied for once the procedure is completed

Berlin, November 25, 2019 – Bayer has submitted an application to the European Medicines Agency (EMA) to extend the Xarelto marketing authorization, making it available for children up to 17 years old with confirmed VTE, including cerebral vein and sinus thrombosis. The application is for the treatment of VTE and prevention of VTE recurrence and builds on the positive results from the phase III EINSTEIN-Jr. study.

This is the largest pediatric study ever conducted for the treatment of VTE and demonstrated a lower occurrence of VTE in children treated with rivaroxaban compared with standard of care (injections of heparin alone or in combination with a vitamin K antagonist such as warfarin). In the EINSTEIN-Jr. study children received rivaroxaban as tablets or as a newly-developed suspension for oral use.

Bayer will apply for a patent extension of six months once the review of the pediatric procedure is completed by EMA and the EU Product Information has been updated. The extension would extend the patent period of Xarelto in Europe to April 2024.
“This application represents an important step towards bringing a new treatment option to children with VTE and at risk of recurrent VTE for whom there are currently limited options,” said Dr Joerg Moeller, Member of the Executive Committee at Bayer AG’s Pharmaceuticals Division and Head of Research and Development. "We look forward to working with the European Medicines Agency to make this treatment available to patients as quickly as possible."

Children with life-threatening illnesses are now living longer healthier lives thanks to advances in medicine, but these children who are often hospitalized for extended periods of time have a higher risk of VTE. Current pediatric treatment of VTE is surrounded by uncertainty as it is largely based on observational data and extrapolation from adult VTE studies. Moreover, the availability of a treatment option that does not require prolonged subcutaneous or intravenous injections and regular monitoring is currently lacking. Injections over an extended period are a huge burden especially for babies and small children. A treatment option such as an oral liquid formulation that does not require injections and regular monitoring will be an important asset in pediatric practice.

VTE includes cerebral vein and sinus thrombosis, a blood clot in the brain, pulmonary embolism (PE), a blood clot that travels to the lung, and deep vein thrombosis (DVT), a blood clot in a deep vein. VTE is an increasingly common complication among hospitalized children with the most common risk factor for VTE being venous catheterization. Currently recommended treatment options for VTE include unfractionated heparin, low molecular weight heparin, and fondaparinux with or without a vitamin K antagonist therapy. No non-vitamin K oral anticoagulant is currently approved for use in this setting.

**About the EINSTEIN-Jr. Study**

The randomized, open-label phase III EINSTEIN-Jr. study included 500 children aged from birth to 17 years with documented acute VTE who had started heparin therapy. The children were assigned, in a 2:1 ratio, to receive body weight-adjusted rivaroxaban (tablets or suspension) in a 20 mg-equivalent dose, or standard of care with unfractionated heparin, low molecular weight heparin or fondaparinux or switched to a vitamin K antagonist. The treatment period was 3 months, but children younger than 2 years with catheter-related VTE received 1 month of treatment. Repeat imaging was carried out at the end of the treatment period. Results were also interpreted in the context of previous studies evaluating rivaroxaban in adults with VTE.
Recurrent VTE occurred in 4 of the 335 (1.2%) children assigned to rivaroxaban and in 5 of the 165 (3.0%) children assigned to standard of care (hazard ratio, 0.40; 95% confidence intervals, 0.11 to 1.41). Repeat imaging showed an improved effect of rivaroxaban on thrombotic burden as compared with standard of care (P=0.012). Clinically relevant bleeding occurred in 10 children (3.0%; all were non-major bleeds) with rivaroxaban and in 3 children (1.9%; two major and one non-major bleed) with standard of care.

About Xarelto™
Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) and is marketed under the brand name Xarelto™. Xarelto protects patients across more venous and arterial thromboembolic (VAT) conditions than any other NOAC:

- 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 pulmonary embolism (PE) in adults
- The treatment of deep vein thrombosis (DVT) in adults
- The prevention of recurrent PE and DVT 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 (CV) death, myocardial infarction (MI) or stroke) after an acute coronary syndrome in adult patients with elevated cardiac biomarkers and no prior stroke or transient ischaemic attack (TIA) when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine
• The prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk for ischaemic events when co-administered with acetylsalicylic acid

• The prevention of venous thromboembolism (VTE) in acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding

Xarelto is approved in more than 130 countries, although the approved labeling, including the number of indications may differ from country to country.

Rivaroxaban was discovered by Bayer, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer and in the U.S. by Janssen Pharmaceuticals, Inc. (Janssen Research & Development, LLC and Janssen Pharmaceuticals, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson).

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

Responsible use of Xarelto 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 about thrombosis, please visit www.thrombosisadviser.com
To learn more about Xarelto, please visit www.xarelto.com

About Bayer
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billion euros. Capital expenditures amounted to 2.6 billion euros, R&D expenses to 5.2 billion euros. For more information, go to www.bayer.com.

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rib (2019-0313E)

**Forward-Looking Statements**
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