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News Release

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Positive CHMP opinion for extension of rivaroxaban marketing authorization to treat venous thromboembolism (VTE) in children

- Pediatric patients currently have limited therapeutic options and until now, there have been no approved oral treatments because of the absence of appropriate clinical trials
- After approval, rivaroxaban would be the only oral Factor Xa Inhibitor authorized to treat VTE and prevent VTE recurrence in children
- An oral suspension of rivaroxaban that does not require injections or regular monitoring has been developed to facilitate pediatric administration
- CHMP opinion is based on the largest pediatric thromboembolism program completed to date, including the phase III EINSTEIN-Jr. study

Berlin, November 13, 2020 – The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion for a marketing authorization extension of the oral Factor Xa inhibitor, rivaroxaban (Xarelto™). Once approved, the use of rivaroxaban will be authorized to treat venous thromboembolism (VTE) and to prevent VTE recurrence in children from birth to below 18 years with VTE, including catheter related thrombosis, cerebral vein and sinus thrombosis.

Currently, there are no approved oral treatments for children with VTE. Rivaroxaban, currently being used in a routine manner in adult patients with VTE, would be the first oral Factor Xa Inhibitor approved for pediatric treatment and prevention of VTE.

“Although advances in medicine mean children with life-threatening illnesses are living longer, healthier lives, those at risk of VTE still have limited treatment options,” said Dr Joerg Moeller, Member of the Executive Committee of Bayer AG's Pharmaceutical Division and Head of Research and Development. “VTE is a very severe complication regardless of age, and therefore appropriate treatment should be available to patients of all ages. With the data from the phase III study EINSTEIN-Jr., rivaroxaban, once

approved, can provide the reassurance of a safety and efficacy profile based on data from the most extensive and comprehensive clinical study program completed to date in pediatric thromboembolism."

Professor Christoph Male from the Department of Pediatrics, Medical University of Vienna in Austria, added: "Availability of the rivaroxaban suspension for oral use will obviate the need for manipulations of adult dosage forms and substantially reduce the number of injections needed for standard anticoagulation treatment and blood sampling. Once approved, the pediatric rivaroxaban regimen will represent an advantageous alternative treatment for children with VTE in the future."

The CHMP positive opinion is based on data from a comprehensive clinical program, including the phase III EINSTEIN-Jr. study - the largest study completed to date investigating the treatment of pediatric patients with VTE.[1] Pediatric VTE typically occurs in children with life-threatening illnesses. Due to frequent hospitalizations for extended periods of time these patients are at an increased risk of VTE. Moreover, current pediatric treatment of VTE is based mainly on observational data and extrapolation from adult VTE studies using injectable heparins and/or Vitamin K antagonists.

During the phase III EINSTEIN-Jr. study, following completion of least 5 days of anticoagulation with heparin children in the rivaroxaban-arm received rivaroxaban, body weight adjusted equivalent to the 20 mg once daily adult dose used to treat deep vein thrombosis (DVT)/ pulmonary embolism (PE). These dosages were administered as tablets or as granules for oral suspension. This study demonstrated a numerically lower incidence of recurrent VTE in children treated with rivaroxaban, compared with standard of care (injections of heparin alone or switched to a vitamin K antagonist such as warfarin). With no difference seen in the primary safety endpoint of major or clinically relevant non major bleeding, the absolute and relative safety and efficacy results seen in the EINSTEIN-Jr. study are consistent with those from previous rivaroxaban studies in adults.[1]

Bayer will apply for a patent extension of six months once the European Commission adopts a decision to update the EU Product Information. The extension would prolong the patent period of Xarelto in Europe to April 2024.

About Pediatric Venous Thromboembolism (VTE)
Pediatric VTE includes cerebral vein and sinus thrombosis (a blood clot in the brain), central venous catheter related thrombosis, pulmonary embolism (a blood clot that travels to the lung), and deep vein thrombosis (a blood clot in a deep vein).

Due to improved treatment and survival rates amongst children with life-threatening or chronic medical conditions, as well as increased awareness among pediatricians, venous thromboembolism (VTE) is being identified more often in hospitalized children.[1] The most common risk factor for VTE in children is 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. There is currently no treatment option for children with VTE that does not require prolonged subcutaneous or intravenous injections or regular monitoring, which can be a substantial burden for small children - especially babies - and also for their parents and caregivers. To address this, Bayer has developed granules for an oral suspension of rivaroxaban that does not require injections or regular monitoring, which will enable precise dosing and easier administration of treatment for children with VTE.

The dose of the oral suspension or the tablets is based on the child's weight. The weight related dose of the oral suspension has been developed to be equivalent to the adult standard dose of 20 mg once daily. Children at least 30 kg or over 30 kg can be treated with either the oral suspension or appropriate rivaroxaban tablets (15 mg or 20 mg).[1]

About the EINSTEIN-Jr. Study
The randomized, open-label phase III EINSTEIN-Jr. study included 500 children aged from birth to below 18 years with documented acute VTE who had started heparin therapy for at least 5 days. Children were assigned, in a 2:1 ratio, to receive body weight-adjusted rivaroxaban (tablets or oral suspension) in a 20 mg-equivalent dose, or standard of care with (low molecular weight) heparin, fondaparinux or vitamin K antagonist therapy. The main treatment period was 3 months, but in children younger than 2 years with catheter related VTE it was 1 month. 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). Major or clinically relevant non-major bleeding occurred in 10 children (3.0%; all non-major bleeds) with rivaroxaban and in 3 children (1.9%; two major and 1 non-major bleeds) with standard of care.

About Rivaroxaban (Xarelto™)

Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) worldwide and is marketed under the brand name Xarelto. Xarelto is approved for 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/or 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 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
- 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 (ASA)

Xarelto is approved in more than 130 countries, although the approved labelling, including the number of indications may differ from country to country. Since launch in 2008, more than 74 million patients have been treated.

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 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 and www.vascularadviser.com

To learn more about Xarelto, please visit www.xarelto.com

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Forward-Looking Statements
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References

[1] Male, C, et al, 'Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial', *The Lancet Haematology,* 7.1 (2019), pp.18-27.