



### VTE Prevention After Major Orthopaedic Surgery:

## **Three Pivotal Phase III Trials Show Superior Efficacy of Rivaroxaban over Standard of Care with Enoxaparin**

- Consistent results across three RECORD trials involving nearly 10,000 patients
- Venous thromboembolism considered the most frequent and potentially fatal complication following major orthopaedic surgery
- No evidence of liver signal attributable to rivaroxaban has been seen

### **Abstract # 6, 307, 308**

**Leverkusen, December 10, 2007** – Phase III clinical trial results released today underscore that the oral, once-daily, investigational anticoagulant rivaroxaban (Xarelto<sup>®</sup>) is significantly more effective than enoxaparin, the standard of care, in preventing venous thromboembolism (VTE) in patients undergoing total hip or knee replacement surgery. Rivaroxaban-treated patients consistently experienced lower rates of VTE events compared to enoxaparin-treated patients across three large studies as well as demonstrating a similar rate of bleeding. Rivaroxaban is being jointly developed by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Data from the RECORD1 and RECORD2 studies, evaluating rivaroxaban in total hip replacement surgery, were presented at the 49th Annual Meeting of the American Society of Hematology. Additional data from the head-to-head RECORD3 study, which showed similar significant results for rivaroxaban over enoxaparin in total knee replacement surgery, were also presented.

The data presented revealed the following results:

- RECORD1 (n=4,541) demonstrated a 70% relative risk reduction (RRR) in total VTE when compared with enoxaparin ( $p<0.001$ ), and an 88% RRR ( $p<0.001$ ) in major VTE.
- RECORD2 (n=2,509) demonstrated a 79% RRR ( $p<0.001$ ) in total VTE when compared with enoxaparin with again an 88% RRR ( $p<0.001$ ) in major VTE.
- RECORD3 (n=2,531) demonstrated a 49% RRR ( $p<0.001$ ) in total VTE when compared with enoxaparin and a 62% RRR ( $p=0.016$ ) in major VTE.
- Bleeding rates were low and similar in all arms.

“In RECORD1, 2 and 3, we have three Phase III trials showing unprecedented results in major orthopaedic surgery for the prevention of VTE and this is genuinely exciting,” said Dr. A.G.G. Turpie, Principal Investigator in the RECORD program, Professor of Medicine, McMaster University, Canada. “In three different trials across large patient populations, we have seen rivaroxaban outperform the current standard of care, enoxaparin, without compromising on safety. This is strong clinical evidence that we are making a major leap forward in oral anticoagulation.”

A key secondary endpoint of the study measuring the reduction of symptomatic VTE, also showed clinically meaningful results in favor of rivaroxaban. For this endpoint, the trials showed an RRR of 45% ( $p=0.222$ ) in RECORD1, an 80% RRR ( $p=0.004$ ) in RECORD2 and a 66% RRR ( $p=0.005$ ) in RECORD3, compared to the standard regimen.

“The symptomatic VTE findings in the RECORD trials are extraordinary,” added Dr. Turpie. “Previous trials were successful in identifying trends towards reducing symptomatic VTE, but with RECORD2 and 3 we are seeing clinically relevant reductions in symptomatic VTE for the first time in orthopaedic surgery. These results are a major milestone in the evolution of anticoagulation therapy.”

Rivaroxaban is a novel, oral, once-daily direct Factor Xa inhibitor in advanced clinical development for a wide range of indications to prevent and treat blood clots. Rivaroxaban works at a pivotal stage in the coagulation process to directly inhibit the enzyme Factor Xa. Based on extensive studies, rivaroxaban has been shown to have a wide therapeutic window without need for routine blood monitoring.

“Bayer Schering Pharma is extremely encouraged by the positive results of the RECORD program which show the potential for rivaroxaban to set a new standard of care in this underserved patient population,” said Dr. Kemal Malik, Head of Global Development and member of the Board of Management of Bayer Schering Pharma AG.

### **Detailed Study Results**

Data presented at the ASH meeting are from RECORD (**RE**gulation of **Co**agulation in major **O**rthopaedic surgery reducing the **R**isk of **D**VT and PE), a global program of four pivotal trials in more than 12,000 patients comparing oral, once-daily rivaroxaban with subcutaneous enoxaparin in the prevention of VTE after elective, major orthopaedic surgery of the lower limbs. Following are summary results from RECORD1, RECORD2 and RECORD3:

#### **RECORD1 (Abstract #6)**

The RECORD1 trial compared the safety and efficacy of rivaroxaban with enoxaparin in patients undergoing total hip replacement surgery. The duration of thromboprophylaxis in both treatments was five weeks. The study showed a 70% RRR ( $p<0.001$ ) in total VTE (composite of deep vein thrombosis, non-fatal pulmonary embolism and all-cause mortality), for patients treated with rivaroxaban compared with those treated with enoxaparin. In addition, an 88% RRR ( $p<0.001$ ) in major VTE (composite of proximal deep vein thrombosis, non-fatal pulmonary embolism and VTE-related death) was observed in patients treated with rivaroxaban. Rivaroxaban demonstrated a similarly low rate of major bleeding to enoxaparin (0.3% and 0.1%, respectively,  $p=0.178$ ).

#### **RECORD2 (Abstract #307)**

The RECORD2 study evaluated the safety and efficacy of rivaroxaban compared with enoxaparin and placebo. The duration of thromboprophylaxis in patients undergoing total hip replacement was 35+/-4 days (extended prophylaxis) for rivaroxaban and 10–14 days for those receiving enoxaparin, followed by placebo. The primary and secondary endpoints were the same as for RECORD1 with a 79% RRR ( $p<0.001$ ) in total VTE and an 88% RRR ( $p<0.001$ ) in major VTE for patients treated with rivaroxaban compared with those treated with enoxaparin. Rivaroxaban demonstrated a similarly low rate of major bleeding to enoxaparin (0.1% and 0.1%, respectively,  $p=0.980$ ).

### **RECORD3 (Abstract #308)**

The RECORD3 trial compared the safety and efficacy of rivaroxaban with enoxaparin in patients undergoing total knee replacement surgery. Enoxaparin was initiated 12 hours before surgery, and rivaroxaban 6–8 hours after surgery; both treatments were continued for 10–14 days. Primary and secondary endpoints were the same as for RECORD1. There was a 49% RRR ( $p<0.001$ ) in total VTE and a 62% RRR ( $p=0.016$ ) in major VTE for patients treated with rivaroxaban compared with those treated with enoxaparin. Rivaroxaban demonstrated a similarly low rate of major bleeding to enoxaparin (0.6% and 0.5%, respectively,  $p=0.774$ ).

Copies of the abstracts may be viewed online at the ASH website:  
[www.hematology.org/meetings/abstracts.cfm](http://www.hematology.org/meetings/abstracts.cfm)

### **Unmet Needs in Venous Thromboembolism (VTE)**

VTE, disease process that begins with a blood clot in a vein, includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients undergoing major orthopaedic surgery are at high risk for VTE because during orthopaedic surgery the large veins of the leg that carry blood back to the heart are damaged, significantly increasing the risk of coagulation and thrombosis.

Each year, approximately 700,000 people elect to have hip and knee replacement surgeries in the U.S. and a blood clot is the most common cause of re-hospitalization for this patient group. In fact, VTE is considered the most frequent preventable serious and potentially fatal complication following major orthopaedic surgery. But the threat stretches beyond orthopaedic surgeries. Blood clots are one of the leading causes of global mortality and a concern for many patient populations, including those with atrial fibrillation at risk for stroke; those at risk for acute myocardial infarction (heart attack); those undergoing major orthopaedic surgery; and acutely medically ill patients.

### **About Rivaroxaban**

To date, rivaroxaban is the most extensively studied oral direct Factor Xa inhibitor in development. Based on the clinical evidence so far, in more than 24,000 patients enrolled in the rivaroxaban development program (of which more than 14,000 have been exposed to rivaroxaban and 2,400 have been treated for 3 to 6 months), no evidence of liver signal attributable to rivaroxaban has been seen. However, a more definite statement can only be made based on availability of the data from long term exposure to rivaroxaban in the

VTE treatment and stroke prevention in atrial fibrillation (SPAF) programs. Almost 50,000 patients are expected to be evaluated in the total clinical development program.

Bayer HealthCare submitted a regulatory filing to the European Agency for the Evaluation of Medicinal Products (EMA) at the end of October 2007 for approval to market rivaroxaban in the EU for the prevention of VTE in patients undergoing major orthopaedic surgery of the lower limbs. Upon regulatory approval, rivaroxaban will be commercialized in Europe by Bayer Schering Pharma. A filing for rivaroxaban for a similar indication in the United States is planned in 2008, where upon approval, it will be commercialized by Scios Inc. and Ortho-McNeil, Inc., both of which are wholly-owned subsidiaries of Johnson & Johnson.

The trade name of rivaroxaban is expected to be Xarelto<sup>®</sup>, pending health authority approval.

### **About Bayer HealthCare**

The Bayer Group is a global enterprise with core competencies in the fields of healthcare, nutrition and high-tech materials. Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Diabetes Care and Pharmaceuticals divisions. The pharmaceuticals business operates under the name Bayer Schering Pharma AG. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Find more information at [www.bayerhealthcare.com](http://www.bayerhealthcare.com).

Bayer Schering Pharma is a worldwide leading specialty pharmaceutical company. Its research and business activities are focused on the following areas: Diagnostic Imaging, Hematology/Cardiology, Oncology, Primary Care, Specialized Therapeutics and Women's Healthcare. With innovative products, Bayer Schering Pharma aims for leading positions in specialized markets worldwide. Using new ideas, Bayer Schering Pharma aims to make a contribution to medical progress and strives to improve the quality of life. Find more information at [www.bayerscheringpharma.de](http://www.bayerscheringpharma.de).

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**Forward-Looking Statements**

This news release contains forward-looking statements based on current assumptions and forecasts made by Bayer Group management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in our annual and interim reports to the Frankfurt Stock Exchange and in our reports filed with the U.S. Securities and Exchange Commission (including our Form 20-F). The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.