

News release for medical media

Rivaroxaban First Oral Anticoagulant to Show Superiority to Enoxaparin 30mg twice-daily in Preventing Blood Clots After Knee Replacement Surgery

New head-to-head Phase III data confirm oral anticoagulant rivaroxaban is significantly more effective than twice-daily injections of enoxaparin in preventing life threatening blood clots after total knee replacement surgery.

RECORD4 confirms findings of previous studies, RECORD1 and 3 in demonstrating rivaroxaban's superior efficacy whilst maintaining similar and low rates of bleeding.

Nice (France), May 30, 2008 – According to data released today at the 9th Annual Congress of The European Federation of National Associations of Orthopaedics and Traumatology (EFORT), the oral, once-daily, anticoagulant rivaroxaban (Xarelto[®]) is more effective in preventing blood clots following total knee replacement (TKR) than twice-daily injectable enoxaparin, the standard treatment regimen in the US, whilst maintaining low major bleeding rates.

The RECORD4 study (**RE**gulation of **Co**agulation in major **O**rthopaedic surgery reducing the **R**isk of **D**VT and **PE**) has shown that rivaroxaban (10mg tablet once-daily) provided TKR surgery patients with a statistically significant reduction of total venous thromboembolism (VTE) event rates over twice daily injectable enoxaparin (6.9% and 10.1%, respectively; $p = 0.012$). This corresponds to a 31% relative risk reduction (RRR) over enoxaparin (30mg injection twice-daily). The rate of major bleeding in the rivaroxaban-treated patients was low and not statistically different to the rate of major bleeding in the enoxaparin-treated patients (0.7% and 0.3%, respectively; $p=0.110$).

"The superior efficacy and similar adverse event profile of rivaroxaban demonstrated in RECORD4 are in line with the outstanding results of the earlier RECORD studies," said Dr. A.G.G. Turpie, Professor of Medicine, McMaster University, Canada and Principal Investigator for

the RECORD program. “The success of this trial strengthens my belief that direct Factor Xa inhibition with rivaroxaban has the potential to revolutionise the way we prevent the formation of dangerous blood clots.”

Mr Ivan Brenkel, Consultant Orthopaedic Surgeon, Queen Margaret Hospital, Fife, added: “It has already been demonstrated in the RECORD 1 & 3 studies that rivaroxaban has superior efficacy to enoxaparin at the European dosing regimen of 40mg once daily. It is particularly impressive that this latest study, RECORD 4, has now demonstrated superiority to the higher dose US regimen of enoxaparin, 30mg twice daily, whilst maintaining similarly low rates of bleeding”.

RECORD4 is part of the global RECORD clinical trial programme, which involved more than 12,500 total hip or knee replacement surgery patients, comparing rivaroxaban with injectable enoxaparin for the prevention of VTE in patients undergoing total hip or knee replacement surgery.

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NOTES FOR EDITORS

About VTE

- Venous thromboembolism (VTE) is a term which encompasses two conditions:
 - Deep vein thrombosis (DVT) – a blood clot in a deep vein (usually the leg) which partly or totally blocks the flow of blood
 - Pulmonary embolism (PE) – an often fatal condition which occurs when part of the blood clot travels to and blocks the arteries in the lungs
- 10% of hospital deaths are caused by VTE, making it the leading cause of hospital deaths¹
- VTE kills up to 60,000 people each year in the UK, a figure that is five times greater than the combined total number of deaths from breast cancer, AIDS, and road traffic incidents¹
- Patients undergoing major orthopaedic surgery, such as hip or knee replacement are at high risk of VTE due to the combination of immobility and surgical trauma

- In November 2007, the All Party Parliamentary Thrombosis Group (APPTG) published a report following an audit of acute hospital trusts which found that only 32% of hospital trusts are taking steps to risk assess patients (for VTE) and bring their practices in line with NICE and government recommendations² which are as follows:
 - Current NICE recommendations state that:³
 - All patients undergoing major surgery should be assessed to identify their individual risk of developing VTE after the procedure
 - All patients undergoing major orthopaedic surgery of the lower limbs should receive anticoagulant therapy, LMWH (low molecular weight heparin) for up to 28 days after surgery in combination with pressure stockings, to reduce the risk of VTE

About RECORD4

RECORD4 compared rivaroxaban with enoxaparin for the prevention of VTE following TKR surgery in 3,148 patients. Rivaroxaban (10mg tablet once-daily) was administered 6-8 hours post surgery, compared to enoxaparin (30mg injection twice-daily) which was administered 12-24 hours post surgery, in accordance with the U.S.-approved regimen.

The study demonstrated a 31% RRR in total VTE, the primary endpoint of this trial (composite of deep vein thrombosis, non-fatal pulmonary embolism and all-cause mortality), for patients treated with rivaroxaban compared with those treated with enoxaparin (6.9% and 10.1%, respectively; p=0.012). Event rates for secondary endpoints were consistently lower in the rivaroxaban-treated patients, but did not reach statistical significance.

About Rivaroxaban

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.

To date, rivaroxaban is the most studied oral, direct Factor Xa inhibitor in development. More than 20,000 patients have been evaluated in the completed Phase II programmes and enrolled thus far in the Phase III programmes. Almost 50,000 patients are expected to be evaluated in total.

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.

The trade name of rivaroxaban is expected to be Xarelto[®], pending health authority approval.

About Bayer Schering Pharma UK

Bayer Schering Pharma is a leading, worldwide speciality pharmaceutical company. Its research and business activities are focussed on the fields of haematology & cardiology, oncology, diagnostic imaging, primary care, specialised therapeutics and women's healthcare. With innovative products and using new ideas, Bayer Schering Pharma aims to make a contribution to medical progress and strives to improve the quality of life of patients.

References

1. Fitzmaurice DA. *BMJ* 2007; 334: 1017-8
2. All-Party Parliamentary Thrombosis Group (APPTG) VTE Research Report, April 19 2007
3. NICE Clinical Guideline 46. Venous Thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. April 2007