csas
Commissioning Support
Appraisals Service

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15th March 2012

National Institute for Health and Clinical Excellence

Dear

RE: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. We are in agreement with the recommendation in the ACD not to recommend rivaroxaban for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.

- **Rivaroxaban was non-inferior to enoxaparin (a low molecular weight heparin) and Vitamin K antagonists (VKA) for the prevention of recurrent DVT,** based on one study (EINSTEIN-DVT), and superior to placebo in an extension trial (EINSTEIN-EXT). Clinically relevant bleeding, defined as the composite of major and clinically relevant non-major bleeding, occurred in about 8% of people in both arms of the EINSTEIN-DVT trial.
- **There were concerns about the generalisability of the research.** The Evidence Review Group (ERG) raised concerns about the generalisability of the EINSTEIN trials to UK practice, as several patient groups were excluded from the study, including those for whom treatment with enoxaparin-VKA is unsuitable. The ERG also raised concerns about the interpretation of 'clinical equipoise' used to assess eligibility into the EINSTEIN-Ext study.
- **The manufacturer of rivaroxaban has included high INR monitoring costs in their model.** The manufacture had estimated INR monitoring costs at £656 per person, including transport costs. The Appraisal Committee has asked the manufacture to provide revised cost-effectiveness analyses assuming less intensive INR monitoring.
- **The precise cost-effectiveness of rivaroxaban is currently unclear.** The Appraisal Committee has asked for further data to allow it to confirm the most likely estimate in general and for sub-groups. Note that the most plausible estimates using the manufacturer's assumptions and a less intensive INR monitoring strategy led to ICERs in the region of £8,000 per QALY gained (for 6 and 12 month treatment duration). This is less than half the £20,000 ICER threshold usually considered a reasonable use of NHS resources.
- **The manufacturer did not model long-term treatment with anti-coagulants, or treatment of recurrent VTE with rivaroxaban.** It is estimated that 20% of patients will require long-term treatment, however treatment beyond 12 months was not considered in the EINSTEIN-DVT trial and the manufacturer did not submit data further than 12 months for patients. The Appraisal Committee has asked the manufacturer to provide a cost-effectiveness analysis of

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long term anticoagulation with rivaroxaban compared with low molecular weight heparin and VKA based on the results of the EINSTEIN-DVT trial.

- **There were concerns about the quality of the research.** The ERG noted several problems with the research, including the exclusion of several patient groups and the composite endpoint of DVT and PE.
- **Clinical criteria used to assign treatments were unclear.** The clinical criteria used to assign treatment durations of 3, 6 or 12 months in the EINSTEIN-DVT trial were not specified. The Appraisal Committee has asked the manufacturer for the clinical criteria/algorithm used and for comments on the differences in the populations in the EINSTEIN-DVT trial.
- **The provisional cost of rivaroxaban is quoted as £2.10 per day and £766.50 annually (per patient).** This is lower than the BNF 63 cost for 10mg rivaroxaban, which is currently approved for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee surgery.
- **Rivaroxaban has the potential to improve some patient's access to treatment.** Rivaroxaban, for example, could increase access to treatment for people of certain religions or beliefs (as low molecular weight heparin is made from porcine heparin), and for patients with poor dexterity or needle phobia. Some people find the regular monitoring and diet restrictions required while on warfarin difficult or inconvenient.