csas
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12th January 2012

National Institute for Health and Clinical Excellence

Dear Ms Joshi,

RE: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

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 prevention of stroke and systemic embolism in people with atrial fibrillation. We are in agreement with the recommendations 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.

- **Adjusted dose warfarin with good control is the most cost effective treatment in patients with atrial fibrillation.** The manufacturer's base-case analysis of rivaroxaban versus warfarin resulted in an incremental cost-effectiveness ratio (ICER) of £18,883 per quality-adjusted life year (QALY) gained. The evidence review group (ERG) identified several limitations with the manufacturer's model, including comparison with populations whose warfarin control (time in therapeutic ratio) was less satisfactory than generally expected in the UK. The ERG presented an alternative base-case ICER of £33,758 per QALY gained.
- **The manufacturer of rivaroxaban has included higher INR monitoring costs associated with warfarin than estimated in the ongoing appraisal of dabigatran etexilate, and these are likely to be higher than the usual costs for NHS patients.** The manufacture had estimated INR monitoring costs at £535 per person. The ERG considered that the manufacturer's cost-effectiveness model was particularly sensitive to assumptions about the cost of monitoring warfarin. This means that if the manufacturer overestimates the cost of warfarin monitoring, this will make rivaroxaban appear more cost-effective. Modelling alternative anticoagulation costs resulted in an ICER for rivaroxaban of £62,568 per QALY. The Appraisal Committee has asked the manufacturer to provide revised cost-effectiveness analyses which incorporates a fixed annual warfarin INR monitoring cost of £242 per person.
- **Time in therapeutic range (TTR) for warfarin should be accounted for in the cost-effectiveness analysis.** In the ROCKET-AF trial, which formed the basis of the manufacturer's submission, the mean TTR for warfarin was 55% (58% median). The ERG considered that this was lower than the TTR generally reported in the UK and in other clinical trials. This would make rivaroxaban appear more effective compared to warfarin as used in the UK, and consequently these results may not be applicable to UK practice. The Appraisal Committee has asked the manufacture to provide revised cost-effectiveness analyses which accounts for the low TTR on warfarin seen in the ROCKET-AF trial.
- **There were other limitations to the generalisability of the research.** The population in the ROCKET-AF trial had more severe disease than the population of UK patients expected to be eligible to receive rivaroxaban. It is unclear whether apparent benefits from rivaroxaban seen in the ROCKET-AF trial would actually be achieved in people with more

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moderate disease. The Appraisal Committee has asked the manufacture to provide a revised model with a baseline risk of strokes and other events more representative of people with AF in the UK. This should be derived from the General Practice Research Database or a UK GP practice-based survey.

- **There were also limitations to the quality of the research.** The results of a single large RCT have been submitted by the manufacturer. The ROCKET-AF trial compared rivaroxaban with dose-adjusted warfarin. The manufacturer submitted a network meta-analysis in people for whom anticoagulation therapy is considered suitable to compare rivaroxaban indirectly with aspirin and dabigatran etexilate. The estimates for rivaroxaban compared with dabigatran etexilate obtained from the network meta-analyses were unreliable and therefore the committee has been unable to say whether rivaroxaban is more effective or cost effective than these alternatives.
- **The provisional cost of rivaroxaban is quoted as £2.10 per day and £766.50 annually (per patient).** This is lower than the BNF cost for 10mg rivaroxaban, which is currently approved for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee surgery. There must therefore be uncertainties about the actual cost of rivaroxaban for the prevention of stroke or systemic embolus to the NHS, and consequently uncertainties about the relative cost-effectiveness of rivaroxaban compared to warfarin in the NHS.
- **Under the proposed indication, all patients with non-valvular AF with $CHADS_2$ score ≥1 would be eligible for rivaroxaban.** This would mean that approximately 1,146 patients per 100,000 would be eligible for rivaroxaban. This is more than the 2006 figures for the number receiving warfarin quoted in NICE's costing report on the management of atrial fibrillation, which suggested that 30% of currently-detected AF cases receive oral anticoagulants, while 36% receive aspirin, equating to approximately 384 patients per 100,000 receiving anticoagulation for atrial fibrillation.

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