NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Appraisal consultation document
Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Comments on the ACD
"Has all of the relevant evidence been taken into account?"

3.18 The ERG's clinical advisers estimated that around 20% of people with deep vein thrombosis would have long-term treatment *because recurrence of venous thromboembolism indicated ongoing risk* (my italics)

Comment: It is assumed that, in the above statement, 'people with deep vein thrombosis' refers to people with a first episode of deep vein thrombosis (DVT). By definition, the best treatment in 100% of people with a proven second or subsequent DVT is long-term anticoagulation. Accordingly, the 'ongoing risk' deemed to indicate long-term treatment in 20% is not only recurrence (which would mandate long-term treatment in 100%) but other factors such as the discovery of certain thrombophilia markers (e.g. antiphospholipid syndrome) or the decision that the initial DVT was unprovoked (idiopathic).

3.21 The ERG noted that composite endpoints would be valid only if the incidence of deep vein thrombosis and pulmonary embolism were expected to be affected equally by the treatment. However, it noted that there could be differential impacts on mortality, costs and quality of life for these two events. *Therefore the validity of the composite endpoints was uncertain*.

Comment: It is agreed that DVT and PE entail 'differential impacts on mortality, costs and quality of life'. However, it is clear from the literature and from experience that an effective treatment reduces the incidence of both PE and recurrent DVT to the same degree, so there is no 'differential impact' in terms of efficacy; i.e. the composite endpoint is valid in terms of efficacy.

3.22 The ERG also noted that anticoagulation with rivaroxaban could increase access to treatment for people of *certain religions or beliefs* (because LMWH is made of heparin from pigs) and for patients with poor dexterity or needle phobia. The ERG also noted that reversal of rivaroxaban is a potential issue because this has not yet been standardised.

Comment: opinions from religious authorities (e.g. a fatwa on the subject in terms of Islamic law from Al Azhar University) have contradicted this statement on several occasions in the context of medical need.

4.7 …The Committee noted that the latter subgroup analysis suggested that rivaroxaban might be less effective than enoxaparin and warfarin in patients for whom 3 months of treatment was pre-specified. The Committee heard from the clinical specialists that they were not aware of any *clinical reasons why rivaroxaban would be less effective in patients who received 3 months treatment*. The Committee heard from the ERG that the lower efficacy in the patient group treated for 3 months was based on a small number of events in both arms and the majority of events occurred in the 6 and 12 month groups. The Committee concluded that there was uncertainty as to whether the relative clinical effectiveness of rivaroxaban in the patients who were assigned 3 months of treatment differed from that seen in the whole trial.

Comment: Not only are there no intelligible clinical reasons for this possible finding, the reverse is the case: it is well recognised that failure to achieve therapeutic INR, as well as bleeding complications, are both more likely to occur during the first 2-3 months of Warfarin therapy. The possible finding therefore seems implausible and likely to be a statistical artefact given the small number of events. It is also difficult to clearly diagnose 'recurrent' DVT in the initial three month period because the initial thrombosis will still be present and the inflammatory reaction (including pain) to it often increases after diagnosis: this may have been misclassified as recurrence in these events.

4.9 The Committee heard from clinical specialists that the advantages of rivaroxaban are its oral formulation, and the lack of need for monitoring (therefore a reduced need for support services). It also heard that rivaroxaban is likely to benefit people who are needle phobic or who want to resume normal patterns of daily life without having to find time to attend clinics. The patient experts highlighted that rivaroxaban is not associated with dietary restrictions and has the potential to increase quality of life for people currently treated with a vitamin K antagonist.

Comment: While the freedom from dietary restrictions is helpful, <u>much more</u> relevant clinically is that rivaroxaban does not have the range of potentially hazardous interactions with entire classes of commonly co-prescribed medications (e.g. antibiotics, amiodarone, etc, etc) that often interferes with warfarin therapy. This contribution to patient safety has been significantly overlooked in this analysis.

4.10 The whether or not to continue therapy. The most commonly used duration of treatment in current practice is 6 months, which corresponds with that used in the largest group in the trial. The Committee noted the written evidence from patient experts, which stated that many people find taking warfarin to be stressful, because of the necessary regular monitoring with blood tests, dosing adjustments, and because people must be careful about their diet because of warfarin's interaction with certain foods. The patient experts expressed the view that rivaroxaban may improve the quality of life of people who currently take with warfarin by removing the need for constant monitoring, frequent blood tests and visits to an anticoagulation clinic.

Comment: see comment on para 4.9. above.

I have no comments to make under the other question headings referred to in the context of the ACD, and no comments on the Evaluation Report.