03 December 2010

NHS
National Institute for Health and Clinical Excellence

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Dear [redacted],

Re: Single Technology Appraisal – Ticagrelor for the treatment of acute coronary syndromes

The Evidence Review Group (ERG; The Liverpool Reviews and Implementation Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 12th November 2010 from AstraZeneca. In general terms they felt that it was very well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 17th December 2010**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Raisa Sidhu – Technical Lead (raisa.sidhu@nice.org.uk). Any procedural questions should be addressed to Kate Moore – Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: General information

Please provide electronic copies of:

A1. The PLATO Study Protocol with any amendments.

A2. The PLATO Study Analysis Plan with any amendments.

A3. The PLATO Clinical Study Report with appendices.

Section B: Clarification on clinical effectiveness

Study conduct

B1. Please clarify how compliance with study treatments was measured (for example pill count returned at each visit or any other method) and please provide the rates of compliance for each arm for each inter-assessment time period of the trial.

B2. Please provide details of the number and type of protocol violations for each arm of the PLATO trial.

B3. Please provide confirmation of details of the adjudication of outcomes specified on page 40 of the submission. Were all outcome events in the PLATO subject to adjudication? If not, what percentage was adjudicated?

B4. Please provide the criteria used to censor patients in each of the presented analyses.

B5. Please expand on the method used for multiple testing, in particular the rationale for the order of the secondary endpoints.

B6. Please confirm if an interim analysis of the clinical efficacy data took place and, if so, how many events had occurred at that time.

Patient outcomes: Key events

B7. Please provide outcomes, including safety endpoints, for the cohort of patients from Europe.

B8. Please provide the results of any analyses that compare rates of bleeding noted between countries or regions.

B9. Please provide Kaplan-Meier survival analysis results for primary and secondary endpoints in the form of numeric tables showing for each event/censored observation:

- the time from randomisation

- the estimated event-free survival (with standard error)

- the number of patients remaining at risk

- the cumulative number of events and

- the cumulative number of censored observations

B10. Please provide more detailed results of primary and secondary endpoints stratified by gender and age, preferably in 10 year bands (for the whole trial population).

Section C: Clarification on cost-effectiveness data

C1. **Priority question:** Please clarify the rationale for the chosen model structure and assumptions in light of the following:

The ERG has commented on the simplicity of economic model and raised concerns that this could hinder the exploration of key issues and provision of robust evidence of cost-effectiveness. The ERG has highlighted that, given the small outcome difference between the treatments, the ICER must be considered vulnerable to small alterations in projection methods, modelling assumptions and parameter values. It notes that the final estimated survival gain is 20 times the initial result reported in the PLATO trial. Since nearly 95% of the estimated benefit is generated by the post-trial Markov model, it is important that this model should be robust and reflect current knowledge of the long-term experience of patients with chronic cardiovascular disease. The ERG has commented that the Markov model is designed with a basic structure which assigns patients to health states on the basis of the occurrence of a first non-fatal MI or stroke event which then governs their future care and mortality until death. There are concerns that this may not reflect the natural history of cardiovascular disease and does not allow for exploration of key assumptions, for example whether early survival gain could be attenuated over time as accumulating patient histories converge. The ERG suggests that a more detailed model reflecting the complex sequence of events suffered by cardiovascular patients over their lifetime could be more appropriate.

In particular, the ERG have noted the following as areas of concern:

- long-term non-fatal event risks are fixed for life and do not reflect known alterations due to ageing, previous (and accumulating) event history, patient type (single or multivascular disease) and disability status (following a severe stroke)

- long-term mortality rates are adjusted for age but not for event history or patient type

- only initial non-fatal MI and stroke events are projected, so that subsequent non-fatal events and all fatal events are not explicitly estimated and no NHS costs are explicitly estimated for them

- implicitly the fatality rates of subsequent events are assumed to be immaterial within the model, though the ERG has shown that fatality is influenced by age, gender, previous event history and patient type.

Baseline Characteristics

C2. Please provide a table showing the following baseline characteristics for each treatment group by each modelled population/sub-population:

- age: mean, standard deviation, minimum, maximum

- proportion with previous history of stroke/TIA

- proportion with previous history of peripheral vascular disease (PAD)

- proportion with substantial/severe disabilty (Rankin scale 3+ or equivalent) at baseline.

Patient Pathways

C3. Please provide separate analyses in the format of Table 6.4 of the manufacturer's submission for sub-groups defined by:

- each modelled subgroup split between:

(i) those patients with a previous history of stroke/TIA and/or PAD and

(ii) those with no such previous history (i.e. only with history of previous cardiac events/diagnosis).

Risk Regression Analysis

C4. Please carry out for each modelled population/sub-population Cox proportional hazards regression analyses of the following events (censored by the other two events and other withdrawals):

- acute MI (fatal and non-fatal combined)

- acute Stroke/TIA (fatal and non-fatal combined)

- other death (not MI or stroke)

Please include the following factors as covariates in the analyses:

- age (in years) at baseline

- gender

- serious/severe disability (Rankin 3+ or equivalent) at baseline

- randomized treatment

C5. Please report regression coefficients for each variate with standard errors and significance level (p-value).