21st July 2011

Professor Carole Longson
Director, Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Professor Longson

Re: Appraisal consultation document on ticagrelor for the treatment of acute coronary syndromes

Daiichi Sankyo UK Ltd and Eli Lilly and Company Ltd appreciate the opportunity to review and comment on the appraisal consultation document (ACD) on ticagrelor for the treatment of acute coronary syndromes (ACS). We welcome that NICE has recognised the value of potent oral anti-platelet medications for patients with ACS.

Our specific comments on the ACD are presented below.

Has all of the relevant evidence been taken into account?
We acknowledge that overall the PLATO trial was a well designed trial with some significant findings. The trial presented clinical data for a broad range of patient subgroups however the concurrent cost effectiveness of these subgroups was insufficiently explored, in particular invasively/non-invasively managed patients as specified in the scope. Identifying the clinical and cost effectiveness benefits in important patient subgroups is of interest to clinicians and patients.

Are the summaries of the clinical and cost-effectiveness reasonable interpretations of the evidence?
In general we consider the clinical and cost effectiveness summaries of ticagrelor to be reasonable interpretations of the evidence presented. However we feel that more detailed cost effectiveness analyses in important patient subgroups would help to ensure appropriate use of this treatment in real life practice.

We agree with the Appraisal Committee's view that the PLATO trial is broadly representative of UK clinical practice except for the proportion of patients that were medically managed in the PLATO trial population. It is estimated that the majority of ACS patients in the UK are medically managed with approximately 15-20% of ACS patients undergoing PCI (estimated from Ludman 2010). In PLATO, only 5216 (28%) of patients were planned to be medically managed and of these, only 3948 patients were truly medically managed (21% of the PLATO trial population) which is a proportion not reflective of UK clinical practice. We question the generalisability of the medically managed PLATO trial population and would usually expect this to be considered given the heterogeneity amongst the ACS population and the differing levels of risk.

The manufacturer has not performed its own indirect comparison of ticagrelor and prasugrel stating it would be difficult due to differences in clinical trial design of the TRITON-TIMI 38 and PLATO studies. The Evidence Review Group (ERG) concurred with this decision. However, the manufacturer used results from an independent indirect comparison (Biondi-Zoccai 2010 - recommended to be viewed with caution due to the inherent differences between the trials) in an economic model to generate an ICER for ticagrelor versus prasugrel. The Evaluation Report states that the economic model used to generate these ICERs was not reviewed by the ERG. We request that the cost effectiveness information of ticagrelor compared with prasugrel (section 3.19) is removed from the guidance as an indirect comparison was deemed inappropriate and the ICER generated using inputs from the independent indirect comparison has not been reviewed by the ERG.

It should be noted that the total mortality analysis is exploratory. The statistical analysis plan for PLATO states that the secondary endpoints should be tested individually in a pre-specified order until the first non-significant difference was found between the two groups. The US Food and Drug Administration (FDA) Advisory Committee Briefing Document for ticagrelor reports that total mortality was the last endpoint to be analysed in the predefined hierarchy and while nominally positive for ticagrelor, formal statistical testing ceased when significance was not reached for stroke (FDA 2010). The exploratory nature of the total mortality analysis is recognised in the ERG report.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Although the provisional recommendations are predominantly based on the appropriate review of the clinical and cost effectiveness evidence presented by the manufacturer for ticagrelor, more specific guidance on the use of ticagrelor in important patient subgroups would be of benefit to clinicians and ensure ticagrelor is used in appropriate patients.

We do not agree that the method for generating ICERs for ticagrelor versus prasugrel was suitable as they are based on an independent indirect comparison which was deemed inappropriate and the analysis was not reviewed by the ERG.

Lastly, we would also like to see further clarification about the proposed date for review. It has been proposed in the ACD that this guidance will be incorporated into forthcoming NICE clinical guidelines on 'The management of myocardial infarction with ST-segment elevation', however this only relates to one aspect of this guidance. Hence, further clarification regarding the proposed date of review for all recommendations would be of interest.

Yours sincerely

[redacted]

References:

Biondi-Zoccai G, Lotrionte M, Agostoni P, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. *Int J Cardiol* 2010: doi:10.1016/j.ijcard.2010.08.035
Ludman PF. BCIS Audit Returns Adult Interventional Procedures: Jan 2009 to Dec 2009. British Cardiovascular Intervention Society, Cardiff October 2010.
FDA Advisory Committee Briefing Document for Ticagrelor June 2010 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220197.pdf