www.lilly.co.uk

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL

Tel: +44 (0) 1256 315000

HTA and Health Outcomes

Medical and Product Information: +44 (0) 1256 315999

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Meindert Boysen
Programme Director, Technology Appraisals
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
1st Floor
10 Spring Gardens
London
SW1A 2BU

Dear Meindert

Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of technology appraisal guidance 182): Daiichi Sankyo UK Limited and Eli Lilly and Company Limited response to the Appraisal Consultation Document (ACD)

Thank you for opportunity to comment on the Appraisal Consultation Document (ACD) on prasugrel with percutaneous coronary intervention (PCI) for treating acute coronary syndrome (ACS).

Whilst we welcome the Appraisal Committee's continued recognition of prasugrel as a valuable treatment option in ACS patients undergoing a PCI for ST-elevation myocardial infarction (STEMI), when stent thrombosis has occurred during clopidogrel treatment and in patients with diabetes in these preliminary recommendations, prasugrel has equally compelling data in the non-ST-segment-elevation myocardial infarction (NSTEMI) patient population who are to undergo PCI:

> In the licensed 10mg population (core clinical cohort) censored at 12 months (EMA recommended length of therapy) the benefit, measured as primary end point, is further improved. Non-CABG-related TIMI major bleeding is ameliorated and is no longer significantly different to clopidogrel. This improved risk of bleeding, together with significantly improved efficacy outcomes resulted in the net clinical benefit being further improved (from HR 0.89 to HR 0.79).[1]

This should support a more positive opinion towards prasugrel use in the NSTEMI ACS population.

Prasugrel offers clinicians a treatment option where a potent oral antiplatelet is considered appropriate for NSTEMI patients, and we urge the Appraisal Committee to reconsider their decision and recommend prasugrel for use in all NSTEMI patients. Not recommending prasugrel in the wider

NSTEMI patient population could mean that optimal treatment is denied to suitable patients. Despite the original decision on prasugrel, and the subsequent decision on ticagrelor, NICE guidance in this complex clinical area has not resulted in consistent opinion amongst clinicians in England and Wales, as confirmed by the clinical experts at the Appraisal Committee meeting. This could lead to a variation in patient care. In addition, the need to treat NSTEMI patients who require a PCI in England and Wales more quickly is a key clinical issue that further supports the availability of potent antiplatelet treatment options. Consistent recommendations for the oral antiplatelets will allow the right patient to get the right medication and in the process generate more evidence that can inform further comparative research to adapt care to improve outcomes.

The Assessment Group's primary analysis showed prasugrel to be a cost effective treatment option when compared to clopidogrel in all the subgroups considered – including ACS patients treated with PCI for Unstable Angina (UA) or NSTEMI without a diagnosis of diabetes mellitus. The Appraisal Committee's decision to make recommendations about cost effectiveness using a five year time horizon is unfair. It is contradictory to the guidance given by NICE in the *Guide to the methods of technology appraisal 2013*[2], and is inconsistent with what has been accepted in previous cardiology technical appraisals and guidelines (TA236 (Acute coronary syndrome – ticagrelor), TA210 (Vascular disease - clopidogrel and dipyridamole), TA182 (Acute coronary syndrome – prasugrel) and CG94 (Unstable angina and NSTEMI)). Another point of inconsistency is the Appraisal Committee's reluctance to accept the extrapolation of the CAPRIE data, while the same and similar extrapolations were accepted in 2010. Finally, the reasoning behind the decision to reduce the time horizon (due to parameters being sensitive to assumptions) is unjustified, considering the robust sensitivity analysis suggests otherwise.

In addition, we commented on the approaches and statements made in the ACD on the following topics:

1. Use of a 5 year time horizon as the base case
2. Prasugrel bleeding rates referred to in the ACD
3. Lack of indirect comparison
4. Base case results in Table 1
5. Correction: Section 4.1.17
6. Correction: Section 4.1.18

Providing guidance that enables physicians and patients the choice of agents (clopidogrel, prasugrel and ticagrelor) in acute coronary syndrome PCI patients in both NSTEMI and STEMI will allow more consistent clinical practice in this complex therapy area and the provision of evidence to support improved outcomes for patients who continue to be at high risk of mortality.

Yours sincerely,

[redacted]
[redacted] **– Lilly UK**

1. Use of a 5 year time horizon as the base case

We have concerns about the Appraisal Committee's decision to make recommendations about cost effectiveness using a 5 year time horizon as the base case on which to base their decision. In using this time horizon, the incremental cost effectiveness ratio (ICER) for the UA or NSTEMI without diabetes subgroup is higher than the range usually considered cost effective by NICE.

This approach conflicts with the guidance given in the NICE's *Guide to the methods of technology appraisal 2013*[2], which states that a lifetime time horizon for clinical and cost effectiveness should be adopted if:

1. a technology has an impact on the costs and outcomes over a patient's lifetime;
2. a treatment affects survival at a differential rate when compared with the relevant comparator.

Following this guidance, it is appropriate that a treatment for ACS have a lifetime time horizon as it affects survival, as well as costs and outcomes over a patient's lifetime. In addition, the decision problem states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs and outcomes between the technologies being compared.

Inconsistency with previous appraisals

A lifetime time horizon has been accepted in other economic models in cardiology, such as those used to inform TA236 (Acute coronary syndrome – ticagrelor), TA210 (Vascular disease - clopidogrel and dipyridamole), TA182 (Acute coronary syndrome – prasugrel) and CG94 (Unstable angina and NSTEMI).

The Appraisal Committee has recognised that extrapolation is often necessary in economic modelling due to limited long term data. Extrapolation based on data collected over 3 years or less is common in cardiology health economics. In the models for TA236 (Acute coronary syndrome – ticagrelor) and CG94 (Unstable angina and NSTEMI), extrapolation was derived from MINAP data, which was collected over 2 years. CAPRIE data was used in TA210 (Vascular disease - clopidogrel and dipyridamole) to estimate long term risk in a lifetime model, and was accepted by the NICE Appraisal Committee. However, the extrapolation of this CAPRIE data (which had a follow-up period of 3 years) is now being questioned in this appraisal.

Sensitivity analysis

A reason given by the Appraisal Committee for their decision to use the 5 year time horizon for the base case is that "…the cost-effectiveness of prasugrel was highly sensitive to changes in key model assumptions". We disagree with this statement. The Assessment Group conducted robust sensitivity analysis, assessing the sensitivity to changes in key model assumptions (both univariately and probabilistically) and clearly showed across all subgroups that the model was not highly sensitive to changes in key model assumptions. The range of the ICER with the univariate sensitivity analysis was generally within £2,000, and values fell well below the range considered to be cost effective by NICE

(£20,000 - £30,000/QALY gained). In the model submitted in TA236 (Acute coronary syndrome – ticagrelor), these univariate ranges included parameters that varied by £30,000.

In addition, our own analysis showed that when looking at values for UA/NSTEMI without diabetes (which had a deterministic incremental cost of £248 and incremental QALYs of 0.053 at 40 years - giving an ICER of £4,667), if the incremental cost is kept constant and the incremental QALYs decreased, a decrease of 85% would be required before the ICER crosses a £30,000/QALY threshold. Likewise, if the incremental QALYs remain constant and the incremental cost increases, the cost would need to increase by seven times before the £30,000/QALY threshold is crossed. Decreasing the QALY gains by 50% as well as increasing the costs by 50% (£496) led to an ICER of £18,717 - an ICER below a £20,000-£30,000/QALY threshold. Such alterations should be considered extreme, but still produce ICERs below the accepted thresholds.

In using the 5 year ICER for prasugrel compared with clopidogrel in patients with UA or NSTEMI without diabetes, the Appraisal Committee concluded that prasugrel was not a cost effective use of NHS resources. This would not have been the case if a lifetime time horizon was used as the base case.

2. Prasugrel bleeding rates referred to in the ACD

It is stated a number of times throughout the ACD that prasugrel use leads to a greater incidence of (potentially fatal) bleeding compared to clopidogrel. These statements are misleading when referring to the bleeding rates observed when prasugrel is used according to its current label.

In the core clinical group, no statistically significant difference in the rate of non-CABG-related TIMI major bleeding was noted between patients in the prasugrel and clopidogrel arms. A significant difference in favour of clopidogrel was only seen when major and minor bleeding events were combined.[3]

In order to be consistent and clear throughout the ACD we suggest that all references in the ACD to the bleeding rates of prasugrel should relate to those observed in the core clinical cohort, as this is the data the recommendations are based on and reflect our licensed indication for the 10mg dose.

3. Lack of indirect comparison

We understand why the Appraisal Committee wanted an indirect comparison between prasugrel and ticagrelor to assist them in the decision-making process. However, key differences in the pivotal trials of prasugrel and ticagrelor mean that a formal indirect comparison is highly problematic and potentially inappropriate.

This lack of comparable data again highlights the need for further experience of all the licensed treatment options available, utilised in similar patients in clinical practice.

4. Base case results in Table 1

We consider it inappropriate to report the ERG amended results from TA182 alongside the current MTA results for three reasons:

1. There is not enough information provided in the documentation for the current MTA or the previous STA (TA182) to replicate the finding for the subgroup UA/NSTEMI without diabetes, as such we are unable to confirm the accuracy of the analysis.
2. It is unclear which cohort (e.g. target patient group, overall ACS group) the subgroup has been drawn from and whether the 'full' subgroup is analysed or a median patient. It appears more likely the median patient has been used, whereas in the MTA model it was run for the entire patient group rather than the median patient. It was acknowledged in the previous TA that this is not appropriate.
3. The MTA process and the STA process, as well as the models used in the assessments are, not equivalent. However, the presentation of the results in Table 1 would not allow a general reader to understand either the difference in the TA process or the concerns that the manufacturer had with the ERG amendments or the concerns that ERG had with the structure of the model, but would suggest these results can be read alongside each other.

5. Correction: Section 4.1.17

Under section 4.1.17 (p. 14) in the ACD it is stated that for patients aged 75 years and older, weighing less than 60 kg or with a history of stroke or transient ischaemic attack there were "…no statistically significant differences between the 2 groups for the primary efficacy end point."

The results for the primary safety end point (non-CABG-related TIMI major bleeding) were not significant either, but this is not explicitly stated in the text.

In order to give a balanced view of the data, the non-significance of both end points should be presented in the same manner.

6. Correction: Section 4.1.18

It is stated under section 4.1.18 (p. 15) in the ACD that "The Assessment Group noted that if the incidence of clinical myocardial infarctions was compared, there may be no differences in outcomes between the treatment arms."

This statement is contradictory to our understanding of the Assessment Group's comments on p. 43 of the Assessment Report[4]. More clarity on what information this statement is based on is required if it is to be included in the ACD.

References

1. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical Outcomes for Prasugrel Versus Clopidogrel are consistent among patients from TRITON-TIMI 38 with Unstable Angina or Non-ST-Elevation Myocardial Infarction. European Heart Journal. 2013 34 (Abstract Supplement), 882
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3. Wiviott SD, Desai N, Murphy SA et al. Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies. Am J Cardiol. 2011 108:905-1
4. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, McEntee J, Dundar Y, Richardson M, Fisher M. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182). The Liverpool Reviews and Implementation Group, The University of Liverpool, 2013