AstraZeneca

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20 July 2011

Dear Carole,

Single Technology Appraisal – Appraisal Consultation Document -Ticagrelor for the treatment of ACS

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). In summary we feel the ACD is comprehensive with provisional recommendations which provide a robust basis for consultation.

In commenting we have responded to each of the specified questions.

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

  While the provisional recommendations provide a suitable basis for guidance to the NHS we would recommend that consideration is given to the following in order to provide further clarification:

  - Specifying that ticagrelor should be used in combination with low dose aspirin
  - Specifying the duration of treatment with ticagrelor as 12 months
  - Amending the recommendation for unstable angina to remove the requirement for diagnosis to be confirmed by a cardiologist

  Low dose aspirin

  In order to reflect the Summary of Product Characteristics we request that the recommendations specify that *'ticagrelor in combination with low dose aspirin is recommended as a treatment option'*.

  Duration of treatment

  The current recommendations make no reference to the duration of treatment with ticagrelor. This may result in a variation in the duration of treatment, with some patients potentially receiving treatment for suboptimal periods and others for periods greater than 12 months, for which a benefit has not yet been established. Both the clinical and cost-effectiveness data submitted and discussed by the Appraisal Committee are based on a 12 month treatment duration with the data clearly demonstrating benefits of ticagrelor in terms of improved efficacy and cost-effectiveness when compared with clopidogrel. We would therefore recommend that in order to improve the current recommendations and

ensure all patients receive treatment for the appropriate duration of time the following statement is added at the end of section 1.1:

'*The recommended treatment duration for ticagrelor (in combination with low dose aspirin) for adults with ACS is 12 months'.*

Unstable angina - Confirming diagnosis

The current recommendation for unstable angina specifies that *'after treatment is initiated it should only be continued if the diagnosis is confirmed by a cardiologist'.* This does not reflect current clinical practice where diagnosis is confirmed by different clinicians according to local treatment protocols. Specifying a cardiologist will require a change to current treatment protocols and a change to clinical practice. It should also be noted that the requirement for a cardiologist to confirm diagnosis is not a requirement within NICE guideline for unstable angina and NSTEMI (CG94). In order to reflect current clinical practice and also avoid confusion with CG94 we would recommend that the current text is revised as follows with reference to a cardiologist removed *'After treatment is initiated it should only be continued if the diagnosis is confirmed ~~by a cardiologist~~'*

- **Has all of the relevant evidence been taken into account?**

  We can confirm that all relevant evidence has been taken into account.

- **Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?**

  While the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence there are a number of areas which would benefit from additional clarification and we have highlighted these in the attached table.

  In addition there are two areas which are factually incorrect and require amending.

  1. The first of these relates to the last sentence in section 3.6 where ticagrelor and prasugrel have been transposed. The sentence should read:

     'Ticagrelor ~~prasugrel~~ was associated with a significantly lower risk of any major bleeding and major bleeding associated with bypass surgery than prasugrel ~~ticagrelor~~'

  2. The second relates to section 3.30 where it states

     '*The ERG acknowledged that the use of healthcare resources was estimated in the model using data from an imbedded health economic study, which collected details of hospital care received by patients during the PLATO trial. However, it noted that these data were collected for only 57.4% of the trial population, and the manufacturer provided no information about how this subset was selected.'*

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This statement is incorrect. Resource use was collected for all patients within the PLATO study, however, for the purposes of the model, only data for the 12 month cohort were used to estimate the one year costs. This ensured that the resource costs accurately reflected a 12-month treatment duration as per the time horizon of the short-term decision tree portion of the model.

'*The ERG acknowledged that the use of healthcare resources was estimated in the model using data from an imbedded health economic study, which collected details of hospital care received by patients during the PLATO trial. ~~However, it noted that these data were collected for only 57.4% of the trial population, and the manufacturer provided no information about how this subset was selected~~. For the purposes of the model, only data for those patients in the 12-month cohort were included . This cohort comprised of patients who, based on timing of enrollment, had the potential to receive 12 months treatment with ticagrelor.*

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

  No

- **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?**

  No

Please do not hesitate to contact myself or [redacted] ([redacted]) should you require any further information or clarification.

We look forward to the further development of the provisional recommendations and the Final Appraisal Determination.

Kind regards,

[redacted]
Market Access

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Clarification comments

Page	Section	Comment
4	2.1	For clarification the final sentence in this section would benefit from the addition of 'medical management' e.g. '*Patients with acute coronary syndromes who receive ticagrelor and aspirin may receive drugs only (medical management) or may also undergo revascularisation with PCI or CABG'*
6	3.2	Again for clarification the final sentence would benefit from the addition of 'CABG' and 'invasive procedure' e.g. '*In the subgroup of patients for whom PCI and CABG (invasive procedure) was planned at randomisation, the first pre-specified end point was the same as the primary endpoint (that is, the composite of myocardial infarction, stroke and death from any cause)'*
6	3.3	While section 3.2 refers to the secondary endpoints of the PLATO study with regards to study design details of the actual results are not presented in section 3.3. In order to inform the reader of these results and also reflect both the AstraZeneca submission and the ERG report we recommend the addition of the following text to the end of section 3.3: *'For the secondary endpoints ticagrelor reduced the incidence of MI (HR [95%CI] = 0.84 [0.75-0.95], p=0.005) and death from vascular causes (HR [95%CI] = 0.79 [0.69-0.91], p=0.001). There was no effect observed on the rate of stroke.* *An exploratory analysis of total mortality identified a lower incidence in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 4.5% per year in the ticagrelor treatment group compared to 5.9% per year in the clopidogrel treatment group (HR [95%CI]) = 0.78 [0.69-0.89], nominal p<0.001)'.*
7	3.5	The current sentence '*Patients randomised to ticagrelor experienced more bleeds (major or*

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		minor) not related to CABG (HR 1.19; 95% CI 1.02 to 1.38; p = 0.03 and HR 1.11; 95% CI 1.03 to 1.20; p = 0.008 respectively' is confusing and does not clearly distinguish between the rates of different bleeds. In order to clearly document the different types of bleeds we would recommend amending the current sentence as follows: '*Patients randomised to ticagrelor experienced more overall major and minor bleeding (HR 1.11; 95% CI 1.03 to 1.20; p=0.008) as well as more major bleeding not related to CABG (HR 1.19; 95% CI 1.02 to 1.38; p=0.03).'*
7	3.5	For clarification in relation to fatal bleeding for the ticagrelor and clopidogrel groups we would recommend the addition of the following sentence, '*Fatal bleeding not attributed to intracranial bleeding was significantly higher in the clopidogrel group (HR not reported; p = 0.03). There was no difference between the two groups in relation to overall fatal bleeding (0.3% in each group).'*
7	3.5	Ticagrelor needs to be added to the following sentence: *'Holter monitoring detected more ventricular pauses of length greater than or equal to 3 seconds during the first week in the ticagrelor group than in the clopidogrel group, but these occurred infrequently at 30 days and were rarely associated with symptoms'.*
8	3.5	In order to accurately reflect the duration increases in serum uric acid and serum creatinine with ticagrelor compared with clopidogrel the following text should be added at the end of section 3.5: *'Patients randomised to ticagrelor had significantly greater increases from baseline in levels of serum uric acid and serum creatinine compared with those on clopidogrel; p < 0.001 for both events throughout the study but there was no difference between the two groups by 1 month following discontinuation of treatment.*

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8	3.6	Within the PLATO study investigators specified whether patients were to receive initial revascularisation – this should be reflected in the current text as follows: *'TRITON-TIMI 38 enrolled patients with ACS who were managed invasively with PCI, whereas in PLATO investigators prespecified whether patients were to receive initial revascularisation or medical therapy alone'*
9	3.6	Within section 3.6 no reference is made to the proportion of patients who underwent CABG in the TRITON and PLATO studies. In order to provide this information to the reader and accurately reflect the data we would recommend the addition of the following sentence at the end of section 3.6: '*The risk of major bleeding not related to bypass surgery did not differ between the prasugrel and ticagrelor groups. CABG accounted for only 3.2% in TRITON compared with 10.2% in PLATO'*
20	4.2	In order to accurately reflect the Appraisal Committee discussions the following sentence should be amended as follows: *'The Committee heard that the dose of clopidogrel does not vary whether a bare-metal stent or drug-eluting stent is used, because all people with ACS undergoing PCI (in the acute setting) are treated with clopidogrel for 12 months'.*

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