Bristol-Myers Squibb

sanofi aventis
Because health matters

Dr Carole Longson
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25th August 2010

Dear Dr Longson,

Re: Review of TA90; Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events

Sanofi-aventis and Bristol-Myers Squibb would like to thank the Appraisal Committee for fully considering the views expressed by the clinical specialists, patient experts and ourselves. We would also like to take this opportunity to thank the Academic group for considering all our comments and especially those regarding the cost-effectiveness results in the Assessment Report.

Sanofi-aventis/Bristol-Myers Squibb welcome the preliminary recommendations of the Appraisal Committee as described in the ACD and look forward to these recommendations progressing to full guidance over the coming months. We are pleased that the Appraisal Committee has included the multivascular patient group, a group at a high risk of further occlusive vascular events, in this review and has provided clear guidance.

Antiplatelets and bleeding risk

Sanofi-aventis/BMS would like to request the deletion of the following line in section 3.2. “There is an increased risk of bleeding from clopidogrel because of its antiplatelet activities.” All antiplatelets, by virtue of their pharmacological properties can increase the risk of bleeding and therefore this is not solely confined to clopidogrel. This is supported by the SmPC of both MRD-ASA and clopidogrel, and the findings of the Academic Group on page 16 of Assessment Report.

Clinical Trials

The Committee considered 4 clinical trials in reviewing the evidence for this appraisal, CAPRIE, ESPS2, which were available before the publication of TA90 and PROFESS and ESPRIT, two newer trials published following TA90.

The CAPRIE trial, comparing clopidogrel with aspirin resulted in a relative risk reduction of 8.7% (p=0.043) in the primary endpoint of first occurrence of the composite outcome of ischaemic stroke, myocardial infarction or vascular death.

The PROFESS study, the largest antiplatelet trial in the secondary prevention of stroke, failed to reach its primary endpoint of recurrent stroke (hazard ratio 1.01, 95% confidence interval 0.92-1.11; p=0.78), but demonstrated that MRD-ASA and clopidogrel are broadly comparable in terms of their efficacy. However when MRD-ASA was compared to clopidogrel there was an increased risk of major haemorrhagic events (HR 1.15, 95% confidence interval 1.00-1.32) and intracranial haemorrhage (HR 1.42, 95% confidence interval 1.11-1.83).

With the publication of PRoFESS, the clinical effectiveness of clopidogrel (75 mg once daily) has been shown to have similar efficacy and a more favourable side effect profile and better tolerability compared with twice daily MRD-ASA. In light of this new evidence from PRoFESS, in addition to the evidence from CAPRIE and comments from the patient experts regarding the value of reducing the number of tablets patients need to take, clopidogrel should be considered the treatment of choice for patients at risk of occlusive vascular events.

Cost-effectiveness

The wider use of clopidogrel in patients at risk of occlusive vascular events is further supported by the economic analyses undertaken by the Academic group which demonstrated that clopidogrel is a cost-effective treatment in this population at the tariff price of £10.90 as per BNF58. The Academic Group conducted analyses utilising both the branded and the generic price of clopidogrel. SA/BMS support the Appraisal Committee's decision to consider the tariff price of clopidogrel as the most relevant for this appraisal. We would like to reiterate that less than 3% of prescriptions written in the NHS are for branded clopidogrel (Plavix) and roughly less than 13% of prescriptions are dispensed as branded clopidogrel (Plavix)[1].

Of special interest is the group of patients who have had an ischaemic stroke. In the Assessment Report received in May 2010, the cost-effective strategy was MRD-ASA followed by ASA, followed by clopidogrel. In our response to that report we pointed out that the costs and QALYS between those treatment strategies with clopidogrel first (e.g. clopidogrel> ASA>MRD-ASA) and those with MRD-ASA first (MRD-ASA>ASA>clopidogrel) were very similar.

The Academic Group ran additional analyses that demonstrated that these differences were small and led to unstable results due to the uncertainty arising from simulation error. The academic model is a patient level simulation where costs and QALYS are estimated over a randomly simulated cohort of patients. The uncertainty arising from simulation error is reduced by increasing the number of simulated patients. Hence, the number of simulated patients was increased from 2,000 to 10,000. This increase resulted in consistent results across runs but also indicated that treatment strategies with clopidogrel as first in the treatment sequence lie on the cost-effectiveness frontier.

The results of the PSA in addendum 3 confirmed the results of the deterministic analysis presented in addendum 2 that treatment strategies with clopidogrel first, lay on the cost-effectiveness frontier. At a WTP =£20,000/QALY the treatment strategies with clopidogrel first in the sequence has an estimated probability of being cost-effective of 68% and at a WTP=£30,000/QALY a probability of 73%.

Of note, these analyses were undertaken at the clopidogrel tariff price of £10.90. This price has subsequently decreased to £5.13[2] which is lower than the price of MRD-ASA of £7.79 and will of course further improve the cost-effectiveness of clopidogrel. We are therefore confident that the preliminary recommendations will remain unchanged and will progress to final guidance over the coming months.

We thank NICE for the opportunity to comment on the ACD and look forward to the Appraisal Committee meeting on the 8th September. In the meantime, if any questions arise sanofi-aventis and Bristol-Myers Squibb will be happy to address them.

Please note that both manufacturers should be contacted in all communications.

Kind Regards,

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[1] IMS BPI April 2010
[2] NICE ACD page 8, July 2010