Bristol-Myers Squibb

sanofi aventis
Because health matters

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

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Dear Dr Longson,

Re: Review of TAG 90; Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events

Thank you for the opportunity to comment on the Assessment Report commissioned for the purposes of this review. We would like to comment on the following content and interpretation within the assessment report:

- the interpretation of the CAPRIE data and the recognition of the MVD population;

CAPRIE was not designed to explore disaggregated outcomes in subgroups, defined by index-events; consequently such analyses have limitations and must be interpreted with caution. This limitation also applies to the subgroup of patients with multivascular disease (MVD), but we welcome their inclusion given their risk of developing subsequent events are much higher than those with a single event history.

- the interpretation and apparent dismissal of the safety conclusions that result from the PRoFESS study;

The PRoFESS study is large enough to allow a direct comparison between clopidogrel hydrogen sulphate and a fixed combination of modified-release dipyridamole and aspirin in patients with stroke, and whilst the results of this study were unexpected, they are extremely informative and should not be dismissed.

- the exclusion of informative trial data from the Mixed Treatment Comparison (MTC);

In our opinion, the MATCH and CHARISMA trials were excluded from the MTC analyses unnecessarily, and these data should have been used to supplement the older CAPRIE data published in 1996.

- the derivation of the pseudo-stroke states from the reported endpoint data;

The characterisation of stroke events into “first ischaemic stroke” and “any recurrent stroke”, has been based on different data sources and this has the unintended consequence of inferring that clopidogrel hydrogen sulphate is more efficacious in preventing the third stroke than it is in preventing the second stroke – a situation which is both anti-intuitive and in contradiction to its license.

- the new economic model developed by the Assessment Group;

The ICER results for the stroke population are very similar (they are similarly effective, and similarly priced), and with only limited sensitivity analyses performed, such low estimates

could not reasonably be considered sufficient to drive different recommendations for the products under assessment.

We would ask that the Assessment Group clarify, i) how their MTC results have been used to inform their cost-effectiveness model, ii) how they modelled a baseline risk and which steps have been taken to estimate the efficacy of other comparators compared to the reference treatment, and iii) how was the TA 90 feature applied to the four subgroups.

- the criticisms of the SA/BMS economic model;

The REACH registry is the most appropriate resource to inform the baseline risk of athrerothrombotic events. The follow-up of this large sample of patients was extensive, making it an ideal dataset for long term extrapolation of events.

The interpretation of the CAPRIE data

The CAPRIE study[1] assessed the cardiovascular benefit and safety of clopidogrel hydrogen sulphate in comparison to aspirin (ASA) in patients with cardiovascular disease whose qualifying ischaemic event (MI, stroke, or PAD) was a manifestation of disease in one or more vascular beds. Evidence suggests that those patients who suffer an MI are at greater risk of a further MI, and those patients who have a stroke are at greater risk of a further stroke, however, a substantial body of evidence has also shown that those initial vascular sites are not the exclusive sites of subsequent vascular events and that such patients remain at risk of future vascular events in multiple sites.

On this basis, CAPRIE was designed with the power to detect a statistically significant difference in the primary composite outcome (stroke, MI or vascular death) in patients with qualifying events being combined. The study was not powered to assess differences in each distinct subgroup (MI, stroke or PAD) and was not powered to analyse each endpoint in isolation either. This would have required a much larger study to detect differences in efficacy.

As such, subgroup analyses of the CAPRIE data have inherent limitations and must be interpreted with caution; more appropriate comparisons and conclusions for each individual subgroup would require more formal evaluation in a randomised controlled trial. This limitation also applies to the subgroup of patients with multivascular disease (MVD), but for whom, the risks for developing subsequent events are much higher[2] than those with a single event history. The Assessment Group recognised the particular clinical concerns for the MVD population, and whilst this is a population that is under-represented within the present TA 90 guidance, a clear rationale for management guidance is indicated in order to reduce their risks of recurrent cardiovascular events.

The interpretation and apparent dismissal of the safety conclusions that result from the PRoFESS study

Considering stroke patients in particular, the PRoFESS study[3] – possibly the biggest trial in secondary prevention of stroke – is large enough to allow a direct comparison of two antiplatelet regimens; namely a fixed combination of modified-release dipyridamole (200 mg twice daily) and aspirin (25 mg twice daily) (MRD-ASA) compared with clopidogrel hydrogen

[1] A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE), CAPRIE Steering Committee, Lancet 1996;348:1329-1339
[2] One-year cardiovascular event rates in outpatients with atherothrombosis. Steg et al JAMA 2007:297(11);1197-1206
[3] Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. Sacco et al NEJM 2008:359

sulphate (75 mg once daily) in patients with evidence of a recent ischaemic stroke. Furthermore, PRoFESS is a contemporaneous study that informs on efficacy and safety in light of improvements in the management and care of stroke patients, certainly more so than ESPS-2 and CAPRIE. The results of this study, whilst unexpected, are extremely informative, yet seem to have been dismissed in the Assessment Report.

The primary outcome (recurrent stroke) occurred in 915 (9.0%) patients in the MRD-ASA group and 898 (8.8%) in the clopidogrel group (hazard ratio 1.01, 95% confidence interval 0.92-1.11; p=0.78), however, the pre-specified non-inferiority test was not achieved. In this, the largest stroke study evaluating antiplatelets for secondary prevention, it appears that MRD-ASA and clopidogrel are broadly comparable in terms of their efficacy. Importantly and seemingly under-represented in the Assessment Report are the relevance of the safety data from the PRoFESS study.

In section 5.2.2 of the Assessment Group report, under adverse events for PRoFESS, discontinuation and headache were mentioned but notably absent are the increased rate of major haemorrhagic event for MRD-ASA compared with clopidogrel (HR 1.15, 95% confidence interval 1.00-1.32) as well as intracranial haemorrhage (HR 1.42, 95% confidence interval 1.11-1.83). Whilst included in Table 5-7, there is no reference to this important safety data elsewhere.

The most recent American and European stroke guidelines include clopidogrel and MRD-ASA as equivalent options and after the PRoFESS trial, experts consider the two regimens to be at least equivalent[4] [5] [6]. In our opinion, the PRoFESS study is a recent and important study that highlights the similarity in efficacy between clopidogrel and MRD-ASA but also distinguishes between the two antiplatelet regimens in terms of safety. On this basis we maintain our assertion that clopidogrel should be considered a first-line alternative to MRD-ASA in patients with ischaemic stroke.

The exclusion of informative trial data from the MTC

The trials informing the MTC in the Assessment Group report are limited to CAPRIE, PRoFESS, ESPS2 and ESPRIT. These trials were used to estimate the relative efficacy of the relevant treatments in a population with a previous stroke. Five main endpoints were estimated, namely stroke, MI, vascular death, all-cause death and bleedings. For the other populations (patients with MI, PAD or MVD) no MTC was conducted.

Two randomized controlled trials estimating the recurrence of atherothrombotic events in a secondary prevention population were not included in the MTC despite the fact that these trials provide new evidence since the original Technology Appraisal (TA90) in 2004 and can further extend the data available for clopidogrel (nb. the CAPRIE trial dates from 1996). The MATCH trial (N=3800 per arm) was designed to assess the relative efficacy and safety of clopidogrel alone (with placebo) against clopidogrel plus aspirin in reducing vascular ischeamic events in patients with recent TIA or ischaemic stroke at a high risk of a recurring atherothrombotic event.

The inclusion of the CHARISMA trial, linking the combination of aspirin and clopidogrel with aspirin alone, would have closed the circle of evidence between clopidogrel and aspirin allowing the coherence in the network to be assessed. More than one third of patients in CHARISMA (N=7800 per arm, with previous stroke or TIA N=2730 per arm) suffered a previous stroke or TIA. The lack of inclusion of these data also resulted in loss of precision in the MTC results as the addition of over 17,000 patients would have resulted in a much stronger evidence base for the comparison of clopidogrel versus aspirin. Comparing the

[4] Digestion of the antiplatelets comparison of PRoFESS: 18-7=1? Algra, Stroke 2009;40:1932-1935
[5] The PRoFESS trial results: what went wrong? International Journal of Stroke 2008 (3):165-166
[6] PRoFESS, Lees Stroke 2009;40:1941

sanofi-aventis/BMS MTC results with the results of the MTC from the Assessment Group results in the following observations:

i) the ranking of the odds ratios for clopidogrel and MRD+ASA versus ASA alone were the same in both MTCs;

ii) for all endpoints the confidence intervals obtained by the Assessment Group were between 50% and 300% wider than the CIs obtained in our own MTC, reflecting (1) the omission of MATCH and CHARISMA in the network, and (2) the split of the stroke events into two separate stroke endpoints estimated with a subset of available trials each;

iii) many confidence intervals in the MTC from the Assessment Group were overlapping "1" indicating no significant differences between the treatments and aspirin, which was not the case in our own MTC (e.g. the endpoints stroke and MI).

The derivation of the pseudo-stroke states from the reported endpoint data

We have noted that the stroke endpoint was divided into "first ischaemic stroke" and "any recurrent stroke". We would like to note that all patients in this 'stroke' cohort had already had a stroke therefore the estimated endpoints are actually "first recurrent stroke" and "second recurrent stroke". The distinction, in respect to treatment effects, between the second and third stroke is likely to be less important than the distinction between first and second stroke.

The trials informing the "first recurrent stroke" were CAPRIE, ESPRIT and PRoFESS whereas the trials informing the "second recurrent stroke" were ESPS2 and PRoFESS. The evidence base was divided over these two endpoints which is highly unusual[7 8 9], and results in small trials (ESPS2 N=1650 per arm and ESPRIT N=1360 per arm) playing a key role in the chain of evidence whereas a large trial (CAPRIE N=3200 per arm) is not used in all analyses.

This is even more surprising as data on second and third stroke were requested by the Assessment Group, and submitted by SA/BMS, but were not used in this analysis; there is therefore no limitation to the inclusion of CAPRIE data in the "second recurrent stroke" endpoint. The splitting up of the evidence base resulted in a loss of power, wide confidence intervals and loss of statistical significance. For clopidogrel this analysis moreover suggested that clopidogrel is more efficacious in preventing the third stroke than it is in preventing the second stroke – which is in contradiction to its SmPC. Finally we noted that in the "second recurrent stroke" endpoint a mix of ischaemic and haemorrhagic strokes were used.

The new economic model developed by the Assessment Group and the insufficient probabilistic sensitivity analysis

We would like to seek some clarifications from the Assessment Group about their model structure:
The NICE reference case stipulates that head-to-head clinical trials should be used where available and that a MTC should be conducted when indirect evidence is available in addition to head-to-head clinical trials. The commonly accepted method is to apply these treatment effects to a baseline risk model, preferably coming from a real-world dataset rather than from the reference arm of a clinical trial. Could the Assessment Group explain how

[7] The York Assessment Report 2004 For the original TA 90
[8] Stroke Prevention – Insights from Incoherence. Kent and Thaler, NEJM Editorial 2008:359
[9] MTC SA/BMS submission dossier Oct 2009

their MTC results have been used to inform their cost-effectiveness model, as the assessment report is unclear in this regard; it would appear that the MTC is not used?

Breaking up randomization should be avoided and it is uncommon to use event rates from single arms of different trials and compare them directly without making any adjustments for baseline characteristics, trial design, and perhaps in this case also year of trial publication. On p67 of the Assessment report, the Assessment Group mentions that "the trials were disparate in terms of their design, patient populations, interventions and definition/reporting of outcomes which means it is difficult to compare outcomes across the trials ..." It seems unlikely, that the Assessment Group has simply taken selected arms from selected trials and compared them against each other. We would like to ask the Assessment Group how they modelled a baseline risk (which is reference treatment) and which steps have been taken by the Assessment Group to estimate the efficacy of the other comparators compared to that reference treatment?

It seems that aspirin and clopidogrel data from CAPRIE have been pooled on repeated occasions and a single risk model is applied for both treatments based on lack of evidence of consistent differences (e.g. p200 for ischaemic stroke endpoint in the MI and PAD populations, p202 for MI endpoint in stroke patients). PRoFESS also included data on ischaemic stroke for clopidogrel, but surprisingly the data on clopidogrel patients in PRoFESS (N= 10,151) were ignored and only (older) CAPRIE data were used to inform the event rates for clopidogrel. This selection of data sources to calculate a treatment's event rates seems arbitrary and has not been justified in the report.

The Assessment Group's de novo economic model is centred on treatment sequences. It is unclear what type of event triggers a switch in drug treatment (refer to p116 § 3 "the current preventive medication is updated if necessary"). Please can the Assessment Group clarify if the occurrence of an atherothrombotic event is the basis for a change medication, or whether a treatment switch is only driven by the all-cause discontinuation data? If this is the latter, then we observe that the discontinuation rates based on randomized clinical trials may be unrealistic.

With regards to discontinuation rates (p117) we noted that exponential survival curves were estimated to model duration of treatment. For MRD+ASA these were based on PRoFESS and ESPRIT whereas for clopidogrel they were only based on PRoFESS, excluding CAPRIE from the dataset. Discontinuation data were however published for CAPRIE.

In the Results section we noted that, for the stroke population, in most scenarios the costs, life years and QALYs of all the treatment sequences including clopidogrel or ASA+MRD are very similar. ICERs are generally very low and we would be cautious in recommending specific treatment sequences including clopidogrel or ASA+MRD over one another. This is also apparent in the plots of the cost-effectiveness frontiers; for example in the cost-effectiveness plane for stroke patients, the point estimates for each strategy are very close. Limited probabilistic sensitivity analyses were conducted. If the Assessment Group had undertaken and plotted the simulations onto a cost-effectiveness plane, overlapping "clouds" surrounding each point estimate would have resulted suggesting that there are no significant differences between the treatment sequences in terms of cost-effectiveness.

The observation of small differences in cost-effectiveness between clopidogrel and ASA+MRD is supported by the conclusions from the clinical section stating that the two treatments are comparable in preventing atherothrombotic events in a stroke population (p55-57). At a comparable cost per year (£132.62 for clopidogrel (tariff price) and £94.78 for MRD+ASA) one might reasonably expect to obtain similar cost-effectiveness results. In addition, safety and compliance issues associated with MRD should raise clopidogrel as a valuable alternative to MRD in this subgroup.

Of note, in April 2010 roughly less than 3% of prescriptions written were for branded clopidogrel (Plavix)[10] [11] and roughly less than 13% of prescriptions were dispensed as branded clopidogrel (Plavix)[10] [12]. Therefore the scenarios using the branded price of clopidogrel are less relevant than those using the new tariff price.

We were also surprised to see the inclusion of the previous TA 90 (treatment with the combination of aspirin and MRD for 2 years after an ischaemic stroke) in the model as this is uncommon and this is the guidance currently under review. Building an older version of this guidance into the model structure would seem counter-intuitive. The original TA 90 cost-effectiveness model compared different scenarios looking at lifetime treatment but also 2 years treatment with clopidogrel or MRD+ASA followed by lifetime of ASA. Would it be possible to clarify whether the inclusion of TA 90 is applied to patients e.g. "clopidogrel– ASA– nothing". If a patient on this treatment regimen is allocated the following time on treatment: "clopidogrel: 3 years – ASA: 2 years – nothing: 10 years" and this patient experiences a stroke after spending 1 year in the model, will this patient then have 1 year on clopidogrel, followed by 2 years on MRD + ASA, followed by 2 years on ASA, followed by 10 years on no treatment? In addition would it be possible to clarify how the TA 90 feature is applied in patients with a history of MI, PAD and MVD? MRD should be used with caution in patients with severe CAD, including unstable angina or recent MI, left ventricular flow obstruction.

The criticisms of the SA/BMS economic model

The "MVD" subgroup in the REACH dataset (labelled "overall polyvascular disease" in the publication), consisted of 10,674 patients of which:

5,339 had a previous MI and a previous stroke

3,264 had a previous MI and diagnosed PAD

939 had a previous stroke and diagnoses PAD

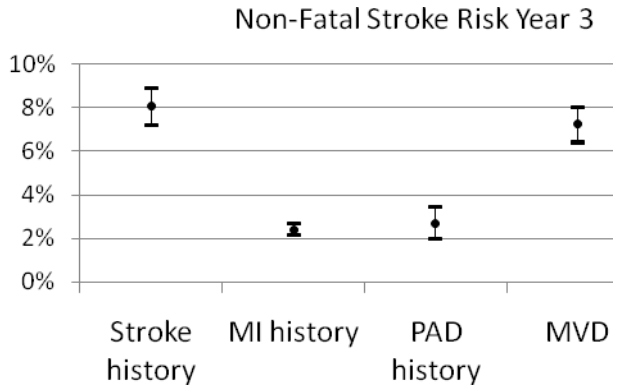
1,132 had a previous MI and a previous stroke and diagnosed PAD

Many of these patients had risk factors in addition to the events already experienced

The REACH data were available separately for year 1, 2 and 3 and the year 3 data were used as the basis for modelling constant event probabilities up to the end of the time horizon of our model. The Assessment Group commented that "extrapolating these transition probabilities for the remainder of the time horizon ... is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations." We would like to highlight that the REACH dataset was very large and patient attrition rates low, resulting in sufficient numbers of patients and events in year 3 to provide estimated baseline event risks with small confidence intervals. The table below displays the sample size for the "nonfatal stroke" endpoint in REACH for the different populations and the accompanying graph displays the confidence intervals around the point estimates.

[10] TNS Scriptcount data April 2010
[11] CSD Patient Data April 2010
[12] IMS BPI April 2010

Population	Year 1	Year 3
Stroke history	10,603	8,104
MI history	28,867	21,456
PAD history	3,246	2,485
MVD	10,674	7,630



We do agree with the Assessment Group that using end-of-trial data (e.g. from CAPRIE or PRoFESS) would have resulted in patient numbers being too low and very volatile, and as a consequence unrepresentative for estimating further events, but we do not believe this is the case with the REACH dataset.

The REACH registry was however, the preferred source of baseline data for aspirin in our model due to its size and time horizon, whilst CAPRIE was used only to calculate relative treatment effects (mean duration of follow-up 1.9 years and N=19185).

The Assessment Group commented that in REACH “only” 67% of patients were taking aspirin monotherapy and secondly that the MVD patients were identified as patients with risk factors of cardiovascular disease. We recognise that 100% aspirin use would have been the preferred data, however the 33% of patients not on aspirin monotherapy, were either on a combination of aspirin with another antiplatelet agent, or on another single antiplatelet agent.

The Assessment Group also commented on page 111 that “none of the effectiveness results used in their [sanofi-aventis/BMS] modelling of cost effectiveness are directly derived from publications from the CAPRIE trial”. We would like to highlight that we presented five separate efficacy analyses: 2 analyses based on an MTC (including the CAPRIE trial) with direct reference to published data, 1 analysis based the PRoFESS trial, 1 analysis based on the CAPRIE publication and 1 analysis based on post-hoc data from CAPRIE, therefore this criticism is unfounded.

Finally, in our submission we used the price for clopidogrel hydrogen sulphate (Plavix) of October 2009. The tariff price for clopidogrel has only recently changed to £10.90. Including this lower price into our cost-effectiveness model would result in clopidogrel being dominant compared to aspirin in stroke patients and MVD patients, and with an ICER of around £2,000 for MI and PAD patients. Compared to the combination of MRD+ASA in stroke patients, clopidogrel would have an ICER of under £500/QALY and therefore clopidogrel should be considered as an alternative to MRD-ASA in this subgroup.

We thank NICE for the opportunity to comment on the assessment report and look forward to the Appraisal Committee meeting on the 8th July. 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,

Sanofi-aventis UK

Bristol-Myers Squibb UK