
Sanofi-aventis and BMS (s-a/BMS) would like to thank NICE for the opportunity to comment on this appraisal at this time. Sanofi-aventis / BMS would like to submit the following comments for consideration.

Summary of comments:
In principle s-a/BMS agree with the preliminary recommendations of the Appraisal Committee in recommending prasugrel as an alternative option for patients with acute coronary syndromes (ACS) having immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction, but only when immediate access to a cath lab is possible and pre-treatment with clopidogrel is not an option. S-a/BMS welcome the recommendation of prasugrel only being started after a true clopidogrel failure to prevent stent thrombosis. However s-a/BMS would caution against the recommendation of switching to prasugrel automatically should a stent thrombosis occur whilst on clopidogrel treatment in ACS. In a real-life setting compliance with medication needs to be explored before switching to prasugrel which may lead to more bleeding.

S-a/BMS agree with the ERG’s assessment of the manufacturer’s submission and with the amendments to the manufacturer’s economic model (as mentioned within the ACD).

The TRITON trial was the main source of clinical evidence in the manufacturer’s submission and was the basis of the economic model. S-a/BMS believe that TRITON is very different to the UK clinical practice and that there are major concerns as to the generalisability of the results in England and Wales. Important differences are expected to be seen with respect to treatment pathways for patients with NSTEMI, UA & STEMI, loading dose for clopidogrel, timing of the initial dose of clopidogrel (pre-treatment with clopidogrel), bleeding rates, relative usage of radial & femoral access routes for PCI, definition of primary endpoint (and especially the definition of myocardial infarction). These issues together with some of the assumptions used in the model (attenuation rates, risk equations and the risk of mortality beyond the trial period) raise significant questions as to whether the effectiveness demonstrated in clinical practice will match the efficacy seen in the TRITON trial, and thus increase the uncertainty around the cost-effectiveness results.
Clinical Evaluation

TRITON & UK Clinical practice (ACD Sections 3.1, 4.3)

The TRITON-TIMI 38 trial is not representative of UK clinical practice and therefore the Appraisal Committee should be cautious in its consideration of the results for the following reasons:

- In the trial most of the patients, (STEMI, and NSTEMI/UA), underwent PCI, whereas in the UK 16% only of the overall ACS patient group will have a PCI. Only 29% of NSTEMI patients and 8% of UA patients will undergo PCI in the UK. Only 12% of STEMI patients will undergo primary PCI while 6% will undergo delayed/rescue PCI. The majority of STEMI patients, 60% will undergo lytic therapy.1

- In the UK roughly 28.1% of PCI are inserted from the radial site whereas in TRITON only 8%2 were from the radial site.

- The timing and administration of loading dose of clopidogrel is not reflective of UK practice or of international guidelines. In the TRITON Study 75% of patients received clopidogrel during or after PCI and are unlikely to have achieved peak platelet inhibitory activity at that time. This may contribute to 23%2 of MIs that occurred in the first hour of the study, under-estimating the benefits that would be expected from clopidogrel. In the UK, NSTEMI patients receive clopidogrel on average 3 days3 prior to PCI. Pre-treatment with clopidogrel has been shown to be beneficial in the PCI-CURE and CREDO studies, with an optimal loading time of 6 hours with a 300mg loading dose. Only about 2% of patients in TRITON were given the study drug more than 6 hours prior to PCI. CREDO showed that if the initial study dose was given between 6 and 24 hours prior to PCI, those patients experienced a 38.6% Relative Risk Reduction in the 28-day primary endpoint (95% CI -1.6%-62.9% p=0.051) compared with no reduction with treatment less than 6 hours before PCI1. In a meta-analysis conducted by Sabatine et al4, pre-treatment with clopidogrel reduced the incidence of CV death, MI or stroke for up to 30 days after PCI regardless of GPIIb/IIIa inhibitor use. Clopidogrel pre-treatment was not associated with a significant excess of TIMI major or minor bleeding.1

- Higher doses of clopidogrel (600mg or more) although off-label are used in the UK and a recent meta analysis by Lotrionte et al5 has concluded that a high clopidogrel loading dose (>300mg) significantly reduces early ischaemic events in patients scheduled for PCI without increased risk of bleeding. The 600mg and 900mg loading doses have been studied in the ALBION trial, in a
NSTEMI population, which demonstrated that the peak level of platelet inhibition achieved by 300mg at 6 hours could be achieved in 2 hours if a 600mg dose was used. Prasugrel at 60mg loading dose, in healthy volunteers, has been shown to achieve a higher peak level of platelet inhibition than 300mg of clopidogrel as early as 30 minutes. The European Society of Cardiology Guidelines on STEMI, support the use of clopidogrel being given as soon as possible to all STEMI patients undergoing PCI. They also support a starting dose of at least 300mg, but state that a 600mg loading dose achieves a more rapid and stronger inhibition of platelet aggregation. The Joint Royal Colleges Ambulance Liaison Committee Guideline Development Group (JRCALC) have developed a drug protocol for the administration of clopidogrel for patients with ST segment elevation myocardial infarction aged 75 years or less. The recommendations, based on current best evidence and expert consensus, state that for patients anticipated to receive thrombolysis, 300mg of clopidogrel orally should be administered; whereas for those who will undergo PCI, 600mg should be administered.

**Stent Thrombosis**

Pre-treatment with clopidogrel has been shown to be beneficial in the PCI-CURE and the CREDO studies, with an optimal loading time of >6 hours with a 300 mg loading dose. In UA/NSTEMI patients in the UK, the average waiting time for going to a cath lab is 3.2 days, which allows for patients to be preloaded well in time. Although off label, the 600mg and 900mg loading doses have been studied in the ALBION trial, which demonstrated that the peak level of platelet inhibition achieved by 300mg at 6 hours could be achieved in 2 hours if a 600mg dose was used. This was achieved in this cohort of 103 NSTEMI patients, with no episodes of severe bleeding and similar minor bleeding rates in all 3 arms. Prasugrel at 60mg loading dose, in healthy volunteers, has been shown to achieve a higher peak level of platelet inhibition than 300mg of clopidogrel as early as 30 minutes.

The TRITON trial was designed such that patients could only be loaded on study drug after a diagnostic catheterisation to check for eligibility for PCI. This resulted in about 3/4 of patients being loaded during or after the procedure was started. Only 2% (approx.) of patients were given the study drug more than 6 hours prior to PCI. This led to most patients in the clopidogrel arm not being optimally pre-treated, which is likely to lead to an over-estimate of the effectiveness of prasugrel when used in the setting of normal UK practice.
The stent sub-analysis of the TRITON-TIMI 38 trial was decided due to concerns about stent thrombosis and put in place by the operations committee before completion of enrolment\(^{16}\). The definitions (Definite/Probable/Possible) used were a modified version of the Academic Research Consortium (ARC) for the trial. The “definite” definition calls for angiographic or autopsy evidence of an occlusion according to the ARC definition.

The review of TRITON by Dr Karen Hicks and presented to the FDA advisory committee\(^{17}\) states that “the CEC (Clinical Endpoints Committee) did not review angiograms and did not review all suspected events of stent thrombosis. In some cases, there was evidence of poor adjudication by the CEC. Furthermore, there was no prospective attempt in TAAL [TRITON] to gather pathological evidence of stent thrombosis. Although 2 autopsies were subsequently obtained and demonstrated stent thrombosis, this limited amount of pathological confirmation of a trial of this size is not adequate.” She concludes that the findings are promising but exploratory and that a randomised, prospective trial should be carried out.

It is also important to note that prasugrel is not indicated for the prevention of stent thrombosis\(^{18}\).

There was a significant reduction in stent thrombosis (definite + probable) in the prasugrel arm compared to the clopidogrel arm (ARR1.3% HR 0.48 p<0.001\(^3\). The majority of this benefit was seen in the early (<30 days) phase, about 1% actual risk reduction, with a very early diverging of the curves.

Early stent thrombosis in particular has been shown to be independently influenced by pre-treatment with thienopyridines. In a formal sub-study of the ACUITY trial\(^{19}\), which enrolled a very similar moderate to high risk ACS patients with an early invasive strategy, involving core laboratory and core qualitative and quantitative analyses of 3405 patients, pre-treatment with thienopyridines compared to no pre-treatment was associated with a halving of the odds ratio of developing a definite or probable stent thrombosis (OR0.49 p=0.02).

A late stent thrombosis benefit (by landmark analysis) was also seen in the prasugrel arm (ARR 0.3% p=0.03) over the 30-450 day period compared to clopidogrel. This benefit however must be balanced with the increase in TIMI major non-CABG related bleeds that also occurs over this period (actual increase in risk 0.4% p=0.028).

Consistently in trials, premature discontinuation of dual anti-platelet therapy has been associated with a higher risk of stent thrombosis, especially in patients with drug
eluting stents. This has led the FDA and NICE \textsuperscript{20} to recommend a duration of 12 months of dual anti-platelet therapy, following drug eluting stent insertion. However, a study of 2360 patients undergoing drug eluting stent implantation showed that 11.1\% of patients discontinued treatment due to “nuisance” or superficial bleeding.\textsuperscript{21} This type of bleeding is not very often captured in clinical trials. TRITON results concentrated on major (>5g/dl drop in Hb) and minor bleeds (3-5 g/dl drop in Hb) which both increased by 32\% and 31\% respectively\textsuperscript{22}. It is likely that “nuisance” bleeding will also increase, thereby increasing the likelihood of premature discontinuation.

We would caution against the recommendation of switching to prasugrel automatically should a stent thrombosis occur whilst on clopidogrel treatment in ACS patients. Compliance with medication needs to be explored before switching to prasugrel which may lead to more bleeding.

\textbf{STEMI patients Primary PCI} \hfill (ACD Section 1.1, 3.7, 4.8, 4.18)

The STEMI cohort of 3,534 patients in TRITON was not designed nor powered to prove superiority over clopidogrel\textsuperscript{23}. This cohort\textsuperscript{24} is made up of 2438 Primary PCI patients and 1094 secondary PCI patients who presented after 12 hours post STEMI and up to 14 days. It is useful to note that thienopyridine use within 5 days was an exclusion criterion for admission into the trial. Of this secondary PCI cohort, only one third had received prior thrombolysis. This secondary PCI group of patients do not conform to any of the treatment pathways for STEMI in the UK.

Patients in the Primary PCI arm had an average symptom to PCI time of 4.2 hours. Only 31\% were given study drug before PCI, in contradiction with UK clinical practice, where ambulance loading of 600mg is recommended by the JRCALC guidelines, with 300mg usually administered at first medical contact if ambulance loading has not occurred.

The STEMI cohort, when considered as a whole, show a 21\% Relative Risk Reduction in the primary endpoint. However, these results are primarily driven by a 35\% Relative Risk Reduction in the secondary PCI cohort. The benefit seen in the primary PCI cohort was not significant at Relative Risk Reduction 13\% (p=0.2662). There were striking differences among the primary PCI and secondary PCI cohorts. Indeed, the bleeding pattern is reversed in the secondary PCI arm \( p =0.07 \), with more bleeds in the clopidogrel arm. In the primary PCI arm, there is a relative increase of 54\% in TIMI major bleeds (non-CABG) in the prasugrel arm compared to
clopidogrel (p=0.11). However for the overall STEMI population the Hazard Ratio for bleeding was 8.19 (p=0.0033)\textsuperscript{16}.

Duration of Therapy

Kaplan-Meier Estimates of the 1\textsuperscript{st} Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations

![Graph showing delta between prasugrel and clopidogrel arms in the UA/NSTEMI and STEMI populations. For STEMI, the advantage begins immediately, reaches its maximum at 18 days, and remains unchanged thereafter. The excess bleeding associated with prasugrel occurs over the length of the 15 month trial.]

The graph above \textsuperscript{25} shows the delta between the prasugrel and clopidogrel arms in the UA/NSTEMI and STEMI populations. For STEMI, the advantage begins immediately, reaches its maximum at 18 days, and remains unchanged thereafter. The excess bleeding associated with prasugrel occurs over the length of the 15 month trial.

The use of prasugrel in Primary PCI, based on these exploratory findings, in trial settings that do not reflect UK clinical practice cannot be recommended. In view of its more rapid metabolism, it does represent an advantage in patients in whom there is no time to pre treat. In areas where preloading occurs in the ambulance, prasugrel may have a limited role. Also, a prolonged duration of therapy may not result in further benefit but may lead to greater bleeding. In those patients who have had a stent placed, especially DES, it may be worth switching to clopidogrel although this hypothesis would need to be tested in a formal trial.
Patients with diabetes (ACD Section 3.8, 4.9)

A pre-specified analysis of TRITON analysed the diabetic and non-diabetic subgroups of the cohort. Although this analysis was pre-specified, enrolment into the study was not stratified according to diabetic status and information regarding diabetes type was post-hoc, leading to a possible imbalance in the clopidogrel and prasugrel populations. Baseline characteristics of the diabetic and non-diabetic subgroups are presented but those of the diabetics on clopidogrel vs. prasugrel are not. The endpoints were the same as with the main trial.

No information is provided regarding the timing of the loading dose in the diabetic cohort. It is important to note that for the whole trial, only about 2% of patients received a loading dose of study drug >6 hours pre PCI procedure.

The design of TRITON was such that appropriate preloading of clopidogrel did not occur. In the CREDO study, where diabetic patients enrolment was stratified and the analysis pre-specified, showed that pre-treatment with clopidogrel (6-24 hours) was largely favourable compared to no pre-treatment (3-6 hours). This trend was also positive in the smaller cohort of diabetics (n=504) in PCI-CURE. In neither of these studies, was there a significant increase in major bleeding (at least 2 unit transfusion).

It is well established that platelets from patients with DM are characterised by increased reactivity, hence the need for appropriate preloading before submitting diabetic patients to PCI. On the basis of this exploratory analysis, it is difficult to recommend prasugrel specifically in the diabetic population. It also raises doubts for the rest of the non-diabetic population who did not derive any significant net clinical benefit, with a significant excess in TIMI major bleeding.

TRITON End point – MIs (Adjudicated vs. Clinical MIs) (ACD Sections 3.17, 4.4, 4.11)

The FDA documents, in the review of TRITON performed by Unger and presented to the FDA advisory committee, show that the Clinical Endpoints Committee (CEC) adjudicated all important endpoint events including MIs, strokes, CV deaths as well as stent thrombosis and bleeding events. For MIs the majority of triggered events (“triggered” by a review of adverse events or lab values) were peri-procedural MIs (PPMIs). PPMIs occurred in asymptomatic patients and were only apparent by biomarker elevation. Also, how these PPMI cases were adjudicated is not clear as the study protocol was changed in January 2006. The ERG report states that only
about 20% of non-fatal re-infarction events within the first 3 days of the trial were diagnosed clinically and that 50% of recorded events were associated with hospital treatment.

The review of TRITON performed by Unger for the FDA\textsuperscript{32} shows that site-reported MIs appeared to be better predictors of death than CEC-adjudicated MIs. Patients with PPMIs in the prasugrel arm had a rate of death comparable to those without MIs. The Table below\textsuperscript{33} shows that absolute mortality is different between the PPMI and MI groups.

The difference between the site reported MIs was 72 (298 clopidogrel vs. 226 prasugrel) reported by the investigators\textsuperscript{34} compared to 145 total adjudicated nonfatal MIs (620 clopidogrel vs. 475 prasugrel).

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In a paper by Akkerhuis et al\textsuperscript{34}, the findings show that there is a difference in mortality rates between PCI-related CK-MB elevation (PPMI) and spontaneous CK-MB elevation (spontaneous MI). Although there is a prognostic implication associated with PCI related events - absolute mortality rates were lower after procedure related infarcts compared with spontaneous infarcts. This should therefore be taken into account in the cost-effectiveness analysis.

While peri-procedural MI is recognised as a prognostic marker, it does not appear to carry the same weight as a spontaneous MI, as demonstrated above. It is unclear how this knowledge will alter the management of an ACS patient who has undergone PCI – as this patient should already be on optimal antiplatelet therapy.
The results for the primary site-reported endpoint are only significant for the unstratified Gehan test and not statistically significant by the log rank test. When stratification is taken into account, no statistical difference is detected by either Gehan or log-rank testing.

In a recently published paper of TRITON using the universal MI classification, the TRITON investigators did not re-adjudicate the MIs based on the universal definition scale but used the pool of already adjudicated MIs, allocating the events to each subtype of the new classification. This does not clarify the issue of how the MIs were initially adjudicated.

**Radial vs. femoral access**

Bleeding in patients with ACS is associated with an increased risk of long-term mortality and morbidity, and this relationship may be causal. Therefore, reducing the frequency of bleeding events is an important goal in the management of patients with ACS. One strategy is the use of the radial artery for access during catheterisation and PCI procedures. A meta-analysis involving 12 randomised trials of trans-radial versus trans-femoral PCI demonstrated similar rates of major adverse cardiac events (OR 0.92, 95% CI 0.57-1.48, P = .7) but an 80% relative risk reduction in bleeding and entry site complications (OR 0.20, 95% CI 0.09-0.42, P < .001).
In the TRITON trial, about 8% of patients underwent a radial PCI procedure\(^2\). In keeping with previous trials, radial access resulted in generally less bleeding than the femoral approach. The trend towards greater bleeding in the prasugrel arm is maintained although the difference between the clopidogrel and prasugrel arms seems less in this post hoc analysis. It should be noted that TIMI major bleed is probably not a very sensitive measure of site bleeding (>5g/dl drop in HB). A more realistic measure would be minor (3-5 g/dl drop) or minimal (<3g/dl drop). Unfortunately, this data has not been presented. It is not known if radial access had any effect on the occurrence of the primary endpoint.

The landmark analysis of TRITON shows an early benefit as well as a continuing benefit over the period of day 3 to month 15. However, within this period, there is a significant increase in non-CABG TIMI major bleeding of 39% and life threatening bleeds of 60%\(^{40, 41}\). These could occur after discharge from hospital, which would lead to primary practice providing care for these patients. While puncture related bleeds may be a cause of non-CABG TIMI major bleeds in the first few days, beyond this time period bleeds are unlikely to be due to access site. As patients seem to be at risk of bleeding even through to the end of the study, the site of access at this point in time is unlikely to be related to the cause of the bleed.
Radial access is accompanied by less bleeding regardless of the agent used but the use of prasugrel is associated with more major bleeding regardless of access site. Since radial access is unlikely to replace femoral access in the near future, the safety profile of prasugrel is unlikely to improve substantially in a real world setting.

**Prasugrel contraindications**  
(ACD Section 2.2)  
Prasugrel is contraindicated in patients with active pathological bleeding, history of stroke or transient ischaemic attack (TIA) and severe hepatic impairment (Child-Pugh Class C). Hence it is important that proper patient history is taken prior to administering prasugrel. We would recommend that this is added to the guidance.

In TRITON patients with prior TIA/Stroke were at higher risk of bleeding with the 10mg maintenance dose compared with the overall trial population and experienced net clinical harm (manufacturer submission p.9). This is important if patients will be given prasugrel in an ambulance setting.

**Economic Evaluation**  
(ACD Section 3.10, 4.11)  
The manufacturer has based the economic model on the TRITON trial, a large RCT. TRITON is not representative of the UK clinical practice, as only a small proportion of ACS patients in the UK will undergo PCI, compared to the trial in which all patients had PCI. Furthermore the timing and the loading dose for clopidogrel in the UK is very different to TRITON, as patients are generally pre-treated and loading doses of higher than 300mg are commonly used. This should be carefully considered by the Appraisal Committee.

The manufacturer has attempted to address only the timing issue for clopidogrel by adjusting the primary endpoints events in the clopidogrel arm of the model during the first three days for the NSTEMI/UA subgroup only. The same adjustment has to be undertaken for the STEMI groups as there is a portion of patients with STEMI that will be pre-treated, in the ambulance, with clopidogrel prior to PCI. Pre-treatment with clopidogrel has been shown to be beneficial in the PCI-CURE and CREDO studies, with an optimal loading time of 6 hours with a 300mg loading dose. CREDO showed that if the initial study dose was given between 6 and 24 hours prior to PCI, those patients experienced a 38.6% Relative Risk Reduction in the 28-day primary endpoint (95% CI -1.6%-62.9% p=0.051) compared with no reduction with treatment less than 6 hours before PCI. In a meta-analysis conducted by Sabatini et al, pre-
treatment with clopidogrel reduced the incidence of CV death, MI or stroke for up to 30 days after PCI regardless of GPIIb/IIIa inhibitor use. With regards to the loading dose, and although CURRENT-OASIS7 has yet to report, a meta-analysis by Lotrionte et al has concluded that a high clopidogrel loading dose (>300mg) significantly reduces early ischaemic events in patients scheduled for PCI without increased risk of bleeding.

Although in the trial only a small proportion of PCIs were performed through the radial artery (only 8% of patients in TRITON had a PCI from the radial site), use of this route is much greater in UK practice (28.1% in the UK). It was stated in the ERG report and the ACD that the bleeding rates for prasugrel may be lower in the UK than those observed in TRITON due to the higher use of the radial site for PCI. As the manufacturer rejected the ERG’s request for data on bleeding rates by access/puncture site, we believe that both clopidogrel and prasugrel will have lower bleeding rates in the UK; a similar reduction of bleeding risk based on the access/puncture site should be applied across both comparator arms.

The primary endpoint in TRITON was a composite endpoint (CE) of CV death, non-fatal MI and non-fatal stroke. The CE occurred in 9.9% of patients in the prasugrel arm and 12.1% of patients in the clopidogrel arm resulting in a hazard ratio of 0.81 which is driven by the non-fatal MIs. Of note, and as stated above, the non-fatal MI endpoint included “clinical” and “non-clinical” MIs. The ERG report states that only about 20% of non-fatal re-infarction events within the first 3 days of the trial were diagnosed clinically and that 50% of recorded events were associated with hospital treatment. Clarification is needed as to how MIs were identified retrospectively and especially after day 4. We strongly believe that both types of MIs are important but there is a lot of uncertainty around the prognosis of the “non-clinical” MIs which will affect the number of future events, hospitalisation rates and costs and the quality of life of those patients. In addition, the question remains as to what proportion of these non-clinical events will be detected in routine care (as compared to systematic screening in the confines of a trial).

**Risk Equations:** *(ACD Section 3.10)*

The manufacturer chose to use multinomial logistic regression analysis to derive risk equations to predict the probability that having experienced an event, the event was fatal or not fatal (non-fatal MI, or non-fatal stroke), instead of using the trial data but no justification was given. As a result if any differences exist between the prasugrel
and clopidogrel arm in the trial then those differences are lost in the economic model and the model results may not mirror the trial results.

The manufacturer used separate regression models to represent the risk of various events from day 0 to 3 (logistic regression), and from 4 day to 15 month (Weibull functions). No theoretical justification was provided.

**Risk of mortality beyond trial period** *(ACD Section 3.10)*

The manufacturer conducted a systematic review to identify sources for the long-term mortality rates for ACS patients which failed to provide the necessary information.

The manufacturer then identified 4 studies of patients who had undergone revascularisation and applied relative risks to UK age and gender specific mortality rates in the model. S-a/BMS concur with the ERG’s report (p62-64) that the four studies are not representative of the current treatment of ACS (1 study based in Sweden in a male population, younger than the one in TRITON, 1 study from the US, 1 NSTEMI population, 1 STEMI population) differ from the TRITON population and therefore should not be used in the model.

**Attenuation of differences** *(ACD Section 4.5)*

The long-term part of the manufacturer’s model assumes that the differences established between prasugrel and clopidogrel in TRITON are preserved indefinitely at the level observed at the end of the trial. As treatment would have ceased for both clopidogrel and prasugrel one would expect that over a 40 year period the differences established in TRITON would become less and less noticeable and that event rates would be similar in both arms.

**Utility values** *(ACD Sections 3.12, 3.19)*

The manufacturer used data from a UK study for the background age-specific population values and then uses a utility decrement from a US study for MI and stroke. As per the ERG’s report (p70-71) S-a/BMS concur that this is inappropriate as they are different national valuations. In addition the adjustments made are not specific to patients that underwent PCI.

S-a/BMS accept the decrement for bleeding used by the manufacturer in the model and agree with the sensitivity analyses undertaken around this. We were unable to identify a better reference in the literature.
Following the PPRS agreement from March 2009 the clopidogrel price has dropped by 3.9%. (75 mg, net price 30-tab pack = £36.35; 300 mg, 30-tab pack = £145.42).

The current cost of a loading dose is £4.85 and a course of treatment for 12 months is £445.90.

1 All UK figures stated from IMS Acute Cardiovascular Analyzer MAT S2 2008
2 ERG report p28
3 BCIS audit returns 2007 www.bcis.org.uk/resources/audit/audit2007
5 Lotrionte et al. Meta-analysis Appraising High Clopidogrel Loading in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol 2007; 100: 1199-1206
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17 P116 FDA advisory committee on prasugrel document
18 Prasugrel Summary of Product Characteristics.
20 NICE Technology Appraisal 152: Drug-eluting stents for the treatment of coronary artery disease p8
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25 Prasugrel Secondary Review by Ellis Unger p 30 Figure 7
27 Steinhubl et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. JAMA 2002;288:2411-2420
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41 Antmann et al J Am Coll Cardiol 2008;51:2028–33
43 Mehta et al. Am Heart Journal 2008; Design and rationale of CURRENT-OASIS 7: A randomised 2x2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST elevation acute coronary syndromes managed with an early invasive strategy. 156(6) 1080
44 Lotrionte et al. Meta-analysis Appraising High Clopidogrel Loading in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol 2007; 100: 1199-1206
45 ERG Report page 65 of 96, NICE STA- Prasugrel for acute coronary syndromes with PCI.