

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention

1 Guidance

1.1 Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary **or**
- stent thrombosis has occurred during clopidogrel treatment **or**
- the patient has diabetes mellitus.

1.2 People currently receiving prasugrel for treatment of acute coronary syndromes whose circumstances do not meet the criteria in 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Prasugrel (Efient, Eli Lilly) is an oral inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of adenosine diphosphate receptors on platelets. Because platelets are involved in starting and/or progressing the thrombotic complications of atherosclerotic disease, inhibiting platelet function can reduce the rate of cardiovascular events such as death, myocardial infarction, or stroke. The summary of product characteristics (SPC) states that

prasugrel, co-administered with acetylsalicylic acid, is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (that is, unstable angina, non-ST-segment-elevation myocardial infarction or ST-segment-elevation myocardial infarction) undergoing primary or delayed percutaneous coronary intervention.

2.2 According to the SPC, prasugrel should be started with a single 60-mg loading dose and then continued at 10 mg once a day for up to 12 months. Prasugrel should be used with caution in patients at increased risk of bleeding, especially in patients who are 75 years or older, people with a tendency to bleed or with body weight less than 60 kg. For full details of side effects and contraindications, see the SPC.

2.3 The manufacturer stated in its submission that the cost of both 5 mg and 10 mg tablets of prasugrel is £47.56 for a pack of 28 tablets. The cost of a loading dose of prasugrel is £10.20 and a course of treatment for 12 months is £628.47 (based on a cost of £1.70 per day for maintenance therapy). Patients would also receive aspirin daily. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of prasugrel and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 Clinical evidence in the manufacturer's submission was taken from a randomised double-blind trial, TRITON-TIMI 38, that compared prasugrel with clopidogrel in 13,608 patients with moderate- to high-risk acute coronary syndromes (unstable angina, ST-segment-elevation myocardial infarction [MI] or non-ST-segment-elevation

MI) who were scheduled to have percutaneous coronary intervention. Patients were given aspirin (at a recommended daily dose of between 75 and 162 mg) in combination with the drugs studied. Patients were randomised to receive a loading dose of 60 mg prasugrel followed by 10 mg prasugrel daily or a loading dose of 300 mg clopidogrel followed by 75 mg clopidogrel daily for up to 15 months (the median treatment period was 14.5 months). After percutaneous coronary intervention, patients received daily maintenance doses of placebo tablets matched to clopidogrel or prasugrel.

- 3.2 The primary efficacy endpoint was a composite of the rate of non-fatal MI, non-fatal stroke or death from cardiovascular causes, during the entire follow-up period. A range of secondary composite endpoints was also included. Major safety endpoints included thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary artery bypass graft (CABG), non-CABG-related TIMI life-threatening bleeding, and TIMI major bleeding (a fall in haemoglobin of 5 g/100 ml or more) or minor bleeding (a fall in haemoglobin of 3 to less than 5 g/100 ml).
- 3.3 The intention-to-treat analysis of the 13,608 patients enrolled in the TRITON-TIMI 38 trial (as reported in the main trial publication) showed that the primary efficacy endpoint was reached in 9.9% of patients in the prasugrel group and 12.1% of patients in the clopidogrel group at 15 months (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.73 to 0.90, $p < 0.001$). There were statistically significant reductions in the prasugrel group compared with the clopidogrel group for rates of MI (7.3% compared with 9.5%, $p < 0.001$), urgent target vessel revascularisation (2.5% compared with 3.7%, $p < 0.001$) and stent thrombosis (1.1% compared with 2.4%, $p < 0.001$). Rates of death for the prasugrel group compared with the clopidogrel group from cardiovascular

causes (2.1% compared with 2.4%, $p = 0.31$) and non-fatal stroke (1.0% compared with 1.0%, $p = 0.93$) were not statistically significantly different between the groups. In the subgroup of patients with an initial non-fatal event, second events were significantly reduced with prasugrel compared with clopidogrel (10.8% compared with 15.4%, HR 0.65; 95% CI 0.46 to 0.92, $p = 0.016$).

- 3.4 Prasugrel statistically significantly increased the rate of TIMI non-CABG major bleeding, which was reported in 2.4% of patients in the prasugrel group compared with 1.8% of patients in the clopidogrel group (HR 1.32; 95% CI 1.03 to 1.68, $p = 0.03$). Life-threatening bleeding occurred at a rate of 1.4% in the prasugrel group compared with 0.9% in the clopidogrel group (HR 1.52; 95% CI 1.08 to 2.13, $p = 0.01$), of which 0.4% were fatal in the prasugrel group and 0.1% in the clopidogrel group (HR 4.19; 95% CI 1.58 to 11.11, $p = 0.002$).
- 3.5 Quality of life was assessed in a substudy of TRITON-TIMI 38 using the Seattle angina questionnaire, angina frequency and physical limitations scores, the London School of Hygiene dyspnoea questionnaire score, and the EuroQoL utility score and visual analogue score. The study planned to recruit 3000 patients, but only enrolled 475 patients.
- 3.6 The manufacturer presented data on subpopulations of the trial, which it referred to as 'licensed' and 'target' populations. The licensed population was defined as the population of patients for whom the drug is indicated in the marketing authorisation, and consisted of 13,090 patients in the TRITON-TIMI 38 trial (518 of the 13,608 patients in the trial had a history of stroke or transient ischaemic attack and were therefore excluded under the marketing authorisation for prasugrel). The target population was the subgroup of patients for whom the full 10 mg maintenance dose of

prasugrel would be considered suitable, specifically patients younger than 75 years, weighing 60 kg or more, and with no history of stroke or transient ischaemic attack.

- 3.7 There were 3421 patients with ST-segment-elevation MI in the licensed population. In this subgroup of patients, the primary efficacy endpoint was reached in 9.8% of patients in the prasugrel group and 12.3% of patients in the clopidogrel group at 15 months (HR 0.79; 95% CI 0.65 to 0.97, $p = 0.02$). The occurrence of non-CABG-related TIMI major bleeding at 15 months was not statistically significantly different between the prasugrel group and the clopidogrel group (2.4% and 2.1%, respectively).
- 3.8 The target population in TRITON-TIMI 38 included 10,941 patients (approximately 80% of the full trial population). In the target population, the primary efficacy endpoint was reached in 8.3% of patients in the prasugrel group and 11% of patients in the clopidogrel group at 15 months (HR 0.66; 95% CI 0.66 to 0.84, $p < 0.001$). Non-CABG-related TIMI major bleeding occurred in 2.0% of the prasugrel group and 1.5% of the clopidogrel group (HR 1.24; 95% CI 0.91 to 1.69, $p = 0.17$).
- 3.9 There were 2947 patients with diabetes in the licensed population. In this subgroup of patients, the primary efficacy endpoint was reached in 12.2% of patients in the prasugrel group and 17.0% of patients in the clopidogrel group at 15 months (HR 0.70; 95% CI 0.58 to 0.85, $p < 0.001$). The occurrence of non-CABG-related TIMI major bleeding at 15 months was not statistically significantly different between the prasugrel group and the clopidogrel group (2.5% and 2.6%, respectively).
- 3.10 The manufacturer conducted a systematic review of relevant economic evidence and a new economic evaluation of the use of prasugrel for patients with acute coronary syndromes having

percutaneous coronary intervention. The evaluation used individual patient data from TRITON-TIMI 38.

- 3.11 The economic model submitted by the manufacturer had a Markov model structure with two phases. The first phase spanned the duration of the TRITON-TIMI 38 trial and the second phase modelled long-term events. Rather than using data from the trial directly in the model, separate risk equations for primary endpoint events were derived from individual patient data from the TRITON-TIMI 38 trial. These risk equations were then used to model events and hospitalisation. Mortality was modelled based on adjustment of population life tables, to reflect the impact on mortality in the long term of the events modelled over the short term. Patients entered the model at the point of experiencing an acute coronary syndrome event, immediately before having percutaneous coronary intervention.
- 3.12 Key efficacy and safety outcomes associated with prasugrel and clopidogrel were included in the manufacturer's economic evaluation. However, the adverse reactions (other than bleeding) reported in TRITON-TIMI 38 were not included in the model as they were considered unlikely to affect the results.
- 3.13 The manufacturer considered that health-related quality of life (HRQoL) data associated with the clinical trial did not provide robust estimates, so it conducted a systematic review to identify HRQoL data relevant to the modelled trial populations. Utility reductions for acute coronary syndromes (0.0409) and stroke/MI (0.0524) were taken directly from a US study, with background UK population norms (free of disease) used to determine utility weights for use in the model. The manufacturer's submission assumed that for a major bleed, a 25% reduction in utility from that of an equivalent (age-adjusted) population was applied for a 14-day period.

- 3.14 In the manufacturer's submission the key categories of estimated costs were related to hospitalisation and drug costs. The total cost of treatment for 12 months would be £628.47 (based on £1.70 per day) for prasugrel and £464.05 (based on £1.26 per day) for clopidogrel. Use of aspirin (75–325 mg daily, £0.01 per day) was modelled over 15 months. The unit cost per hospitalisation for prasugrel was assumed to be the same as for clopidogrel (£2619), rather than using the lower weighted average from data collected in the trial (£2530).
- 3.15 The manufacturer identified two errors in its model after the ERG had concluded its critique of the manufacturer's submission. Unless stated otherwise, the results presented below are based on updated analyses from the manufacturer.
- 3.16 For the licensed population, the manufacturer reported an ICER of £159,358 per quality-adjusted life year (QALY) gained for a time horizon of 1 year and an ICER of £3435 per QALY gained for prasugrel compared with clopidogrel for a time horizon of 40 years. For prasugrel compared with clopidogrel, the manufacturer reported ICERs of £3461 per QALY gained for the target population, £1441 per QALY gained for patients with diabetes and £2167 per QALY gained for patients with ST-segment-elevation MI (£4494 per QALY gained for unstable angina and non-ST-segment-elevation MI). These revised ICERs from the corrected model were not substantially different from the ICERs in the original submission, which were £3220 per QALY gained for the licensed population and £3250 per QALY gained for the target population.
- 3.17 Cost-effectiveness results at a time horizon of 40 years (original uncorrected model) were also presented for selected subgroups and for sensitivity analyses. Analyses carried out to explore the impact of the lack of preloading of clopidogrel used available data from the unstable angina and non-ST-segment-elevation MI

subgroup and reduced the cardiovascular event rate for the clopidogrel arm in the first 3 days. This increased the ICER from £6382 (no adjustment) to £9845 per QALY gained (for a 50% adjustment) and £22,727 per QALY gained (100% adjustment, that is, equivalence between clopidogrel and prasugrel). These sensitivity analyses used a feature of the manufacturer's model which permitted analysis of a single patient profile, referred to as the 'median' patient profile. The median profile was taken from the individual patient data set and selected on the basis of net monetary health benefit analysis. According to the manufacturer, selection was based on the 50th percentile net monetary health benefit resulting from the base-case analysis (at a threshold of £20,000 per QALY gained). The characteristics of the median patient (such as age, gender and whether the patient had diabetes) determined the costs and effects predicted by the model. In other sensitivity analyses halving the relative risk for all-cause mortality for the 'median' unstable angina and non-ST-segment-elevation MI profile increased the ICER from £6,382 to £10,710 per QALY gained.

- 3.18 The ERG stated that the TRITON-TIMI 38 trial used in the manufacturer's submission had followed robust methods and was suitably powered to show a clinically significant difference in the primary efficacy endpoint between the treatment groups. Appropriate specified subgroup analyses and post hoc exploratory analyses were carried out. However, the ERG noted that there was only one relevant randomised controlled trial (TRITON-TIMI 38) which compared prasugrel with clopidogrel in patients treated with percutaneous coronary intervention. It considered that the composite endpoint for primary efficacy required further justification and questioned whether the results of the trial could be generalised to clinical practice in England and Wales. The ERG observed that differences in efficacy between prasugrel and clopidogrel in the

TRITON-TIMI 38 trial were largely because of statistically significant differences in non-fatal MI, which included both symptom driven, clinically detected MI (referred to as 'clinical MI') and MI based on biomarkers and ECG readings (referred to as 'non-clinical MI'). It commented that if only clinical MIs were compared between treatment arms, there may be no difference between prasugrel and clopidogrel. The ERG stated that the loading dose of clopidogrel (the quantity administered and the timing of the dose) used in the trial did not reflect current clinical practice in England and Wales. It also commented that the bleeding risk associated with prasugrel in the TRITON-TIMI 38 trial may have been higher than that experienced in clinical practice, because there was a growing trend in England and Wales to perform percutaneous coronary intervention by radial artery access.

- 3.19 In summary, the ERG considered prasugrel and clopidogrel to be broadly equivalent in terms of clinical effectiveness at 15 months for patients with acute coronary syndromes having percutaneous coronary intervention.
- 3.20 The ERG identified six key areas where corrections or adjustments to the economic model were required. These included life table calculations, discounting, treatment costs, utility values, long-term relative risk of mortality and incidence of non-fatal recurrent MIs. The ERG stated that, taken together, these corrections and/or adjustments would increase the ICER for all patient populations. The ERG was unable to generate model results based on the full model population (including individual patient data on more than 13,000 patients) because of the processing time associated with running analyses in the original model. Therefore, the ERG's exploratory analyses were based on the specified typical/median patient profiles used by the manufacturer for some subgroup and sensitivity analyses (see section 3.16). The corrected manufacturer

cost-effectiveness estimates were received just before the ERG had concluded its report. Unless specified otherwise, all results reported by the ERG were based on the manufacturer's original model. The ERG's exploratory analyses reported that at a time horizon of 1 year, clopidogrel dominated prasugrel (prasugrel offered no additional benefit and was more expensive) for all typical patient populations, except patients with diabetes. At a time horizon of 40 years, for a typical/median patient the original manufacturer's model estimated an ICER for prasugrel of £5751 per QALY gained compared with clopidogrel. Revision of treatment costs reduced the ICER for prasugrel compared with clopidogrel to £4015 per QALY gained. Using alternative utility data resulted in an increased ICER of £6648 per QALY gained. Amending the relative long-term risk of mortality increased the ICER to £12,288 per QALY gained. Reducing the incidence of non-fatal recurrent MI resulted in an ICER of £11,515 per QALY gained. Combining all of the above adjustments in the ERG analyses resulted in an estimated ICER of £20,475 per QALY gained for the licensed population and £20,247 per QALY gained for the target population.

- 3.21 The ERG advised that interpretation of the ICERs presented in the manufacturer's submission was dependent on the full acceptance of the manufacturer's assumptions about long-term mortality projections.
- 3.22 The ERG stated that the following key uncertainties in the underlying clinical evidence had not been addressed by its exploratory analyses:
- The extent to which patients in the trial would have benefited clinically (through reduced MIs) from a higher loading dose and pretreatment with clopidogrel was uncertain.

- Practice in the TRITON-TIMI 38 trial did not reflect the growing trend in England and Wales for percutaneous coronary intervention to be performed by radial artery access. The ERG referred to evidence that major bleeding rates are reduced when percutaneous coronary intervention is performed by this route.
- As incremental health gains for prasugrel compared with clopidogrel were small, the resulting ICERs were highly sensitive to changes in the relative benefits of prasugrel and clopidogrel.

3.23 In response to consultation on the preliminary guidance, the manufacturer provided further results from its economic model. Its analyses were intended to reflect the exploratory analysis conducted by the ERG (section 3.19), but using the whole licensed population, rather than using the typical/median patient profile available within its model. Exploratory analysis using alternative utility data, while also reducing the incidence of non-fatal recurrent MI, resulted in an ICER of £5697 and £8450 per QALY gained for the licensed population and unstable angina/non-ST-segment-elevation MI patients respectively. Amending the relative long-term risk of mortality in addition to using alternative utility data and lower incidence of MI reduced the ICER to £5185 and £7718 per QALY gained in the licensed population and unstable angina/non-ST-segment-elevation MI patients. Varying the relative risk for prasugrel compared with clopidogrel in the first 3 days (in order to explore the effect of preloading clopidogrel), combined with the adjustments to utility data, recurrent MI and mortality, resulted in ICERs of £5709 and £9627 per QALY gained for the licensed population and unstable angina/non-ST-segment-elevation MI patients respectively, when allowing for a 50% adjustment to account for lack of preloading with clopidogrel. No ICER was provided for when full equivalence in the first 3 days was assumed to adjust for the lack of clopidogrel preloading in the TRITON-TIMI 38 trial.

3.24 The ERG stated that the adjustment to the long-term relative risk of mortality by the manufacturer did not match the adjustments implemented for the ERG typical/median patient analysis. The ERG also presented two further sets of exploratory subgroup analyses conducted with the manufacturer's (corrected) model, but omitting the first 3-day preloading adjustment. Subgroups considered were patients with ST-segment-elevation MI or non-ST-segment-elevation MI, divided further into patients with or without diabetes. One set of subgroup analyses produced results based on the manufacturer's 'base-case' model (without ERG adjustments), the other produced results based on the ERG exploratory analysis (see section 3.19). These analyses indicated lowest ICERs in ST-segment-elevation MI patients with diabetes, both with and without ERG adjustments (£1805 and £1146 per QALY gained respectively). With the ERG adjustments, results were £3005 and £6616 per QALY gained in non-ST-segment-elevation MI patients with diabetes and ST-segment-elevation MI patients without diabetes respectively. The ERG-amended model produced a particularly high ICER of £136,888 per QALY gained in the subgroup of patients with non-ST-segment-elevation MI and no diabetes. None of the ERG analyses included adjustment to account for lack of clopidogrel preloading compared with standard clinical practice in England and Wales (see section 3.16).

3.25 Full details of all the trials are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of prasugrel, having considered evidence on the nature of acute coronary syndromes and the value placed on the benefits of prasugrel by people with the condition,

those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee considered the evidence presented by the manufacturer on the clinical effects of prasugrel compared with clopidogrel for the treatment of patients having percutaneous coronary intervention. The Committee noted that the submission was based on the results of a single large trial, TRITON-TIMI 38, which reported statistically significant reductions in a composite endpoint, non-fatal MI and stent thrombosis, but an increased rate of major bleeds (including fatal bleeds) in patients allocated to prasugrel compared with clopidogrel. Overall, all-cause mortality, cardiovascular death and non-fatal stroke did not differ statistically significantly between groups in the trial.
- 4.3 The Committee noted the evidence submitted and presented by the patient experts and clinical specialists. It heard that, overall, prasugrel may be a useful addition to the treatment options available. It has a potentially key advantage over clopidogrel in some circumstances because of its faster antiplatelet action and less variable response. However, the Committee also noted that prasugrel increased the chance of (potentially fatal) bleeding, compared with clopidogrel.
- 4.4 The Committee identified three main areas of uncertainty in the evidence for the clinical effectiveness of prasugrel compared with clopidogrel. Firstly, the Committee heard from clinical specialists that clopidogrel is administered to patients several hours before percutaneous coronary intervention (preloading) in most procedures carried out in England and Wales. Additionally, the preloaded dose of clopidogrel is often 600 mg. This dose and timing of clopidogrel differed from that used in TRITON-TIMI 38 in

which 300 mg (as in the marketing authorisation) was given, without preloading. The Committee therefore considered that more cardiovascular events could have occurred in the clopidogrel group in the trial than might be experienced in a similar cohort of patients having percutaneous coronary intervention in routine clinical practice in England and Wales. As a result, the advantages of prasugrel over clopidogrel in preventing cardiovascular events may have been overstated in the manufacturer's submission, especially for non-ST-segment-elevation MI patients for whom there would be adequate time to give a preloading dose of clopidogrel.

4.5 A second issue concerning the clinical data in the manufacturer's submission was the use of a composite endpoint that included non-clinically detected MIs. The Committee noted that the main positive result in favour of prasugrel was a decrease in non-fatal MIs including non-clinical MIs, which would have increased composite endpoint event rates reported in the trial. The Committee considered that it was not clear if any statistically significant differences would remain between prasugrel and clopidogrel without including non-clinical MIs. In its comments on the preliminary guidance, the manufacturer stated that non-clinical MIs have a similar prognosis to clinical MIs and should therefore be considered equally. The Committee considered that this was unproven and because of the difficulty in relating the results of the TRITON-TIMI 38 trial to clinical practice in England and Wales it was therefore difficult to determine the relative effectiveness of prasugrel compared with clopidogrel.

4.6 A third issue discussed by the Committee concerned the long-term effects of prasugrel. It noted that the clinical trial follow-up was limited to 15 months, but the manufacturer's model extrapolated outcomes to 40 years. Although extrapolation is necessary in modelling, the Committee agreed that in circumstances where the

short-term clinical data lacked certainty, such extrapolation could only increase overall uncertainty. The Committee was mindful of the ERG report which stated that the methods for projecting future survival were based on evidence from different sources and lacked relevance to current clinical practice. The Committee also noted the ERG view that the model may have overestimated the number of long-term deaths and non-fatal MIs prevented because the manufacturer applied historical data from people with clinical MIs (alone) to the risks of death from the combination of both clinical and non-clinical MIs in TRITON-TIMI 38.

- 4.7 The Committee concluded that TRITON-TIMI 38, though well conducted, was not wholly applicable to current clinical practice in England and Wales. The Committee also noted that the use of a radial artery for percutaneous coronary intervention access was associated with reduced bleeding complications and was increasingly used in England and Wales. It agreed that using the femoral artery in the trial rather than the radial artery may have disadvantaged prasugrel, but in most aspects the design of the trial favoured prasugrel. When also considering the absence of preloading with clopidogrel, the limitations of the endpoints used, the uncertainty about the projection of benefits in the long term as well as the greater incidence of bleeding adverse events with prasugrel, the Committee agreed that there was considerable uncertainty about whether prasugrel was clinically superior to clopidogrel in terms of net clinical benefit for the licensed or the target population as proposed in the manufacturer's submission. The Committee therefore considered whether there were any identifiable subgroups of patients for whom prasugrel might show clear superiority over clopidogrel. These potential subgroups included: patients with ST-segment-elevation MI who required urgent primary percutaneous coronary intervention; patients with diabetes; patients at high risk of stent thrombosis, including

patients with clopidogrel 'resistance' (who experience less inhibition of platelet function); and patients treated with clopidogrel who were also taking proton pump inhibitors.

- 4.8 The Committee considered the clinical evidence for prasugrel in the subgroup of patients with ST-segment-elevation MI. In these patients there is only a short time between diagnosis and primary percutaneous coronary intervention. The Committee considered the subgroup results presented in the manufacturer's submission. These indicated a trend towards benefit in ST-segment-elevation MI patients across endpoints even though the primary composite endpoint for ST-segment-elevation MI patients having primary percutaneous coronary intervention was not statistically significant in the clinical trial results. The Committee noted from the clinical specialists that the onset of antiplatelet activity was more consistent and faster with prasugrel than with clopidogrel. The delayed onset of antiplatelet activity with clopidogrel was of particular concern when immediate percutaneous coronary intervention was required because there would be little or no time to give a preloading dose of clopidogrel. The Committee, taking all the above factors into consideration, agreed that prasugrel could have a valuable advantage for ST-segment-elevation MI patients who need immediate primary percutaneous intervention.
- 4.9 The Committee then considered the use of prasugrel compared with clopidogrel in patients with diabetes mellitus who were having percutaneous coronary intervention. It noted that the manufacturer's submission indicated that in patients with diabetes, prasugrel reduced the rate of non-fatal MI, non-fatal stroke or death from cardiovascular causes compared with clopidogrel to a greater extent than for the licensed population (of patients with diabetes and without diabetes). The Committee, mindful of the views expressed by the clinical specialists, considered that lack of a

preloading dose, combined with the lower dose of clopidogrel used in the trial than in current clinical practice, may have disadvantaged clopidogrel in the diabetes population. It agreed, however, that diabetes represented an important and definable risk factor for more severe cardiovascular disease and greater risk of cardiovascular events during and after percutaneous coronary intervention. The Committee therefore concluded that it would be appropriate to consider prasugrel for the treatment of people with diabetes mellitus having percutaneous coronary intervention.

4.10 The Committee heard that clopidogrel-resistant patients (that is, patients whose platelet levels do not respond adequately to the dosage of clopidogrel they are treated with) may be at risk of further cardiovascular events if their treatment is not adjusted by considering a different dosage of clopidogrel or use of other treatments. The clinical specialists described several procedures for testing response to clopidogrel and potentially adjusting treatment. The Committee noted these issues, but was mindful that that there was little evidence for testing clopidogrel response and adjusting treatment and that such testing was not part of routine clinical practice. It noted from the clinical specialists that a clear exception to these concerns was the group of patients in whom stent thrombosis had occurred despite clopidogrel treatment. These patients could reasonably be considered at high risk of further cardiovascular events, are clearly identified, and could therefore potentially benefit from the option of treatment with an alternative such as prasugrel.

4.11 The Committee carefully considered whether a subgroup of patients at high risk of stent thrombosis could be defined. The Committee noted comments from consultees, which proposed that prasugrel be considered for patients who are at high risk of stent thrombosis based on the presence of clinical factors, angiographic

factors and factors related to percutaneous coronary intervention. The Committee noted that identifying patients at high risk would have value in preventing cardiovascular events and death, but was mindful that no validated system for determining high risk was currently available. Furthermore, even if such groups could be identified, evidence on the relative effectiveness of prasugrel compared with clopidogrel would be required. The Committee was also mindful of the adverse events (bleeding) and that the balance of adverse events and potential benefits of prasugrel was uncertain across patient subgroups. The Committee concluded that there was insufficient evidence to support recommendations based on risk factors for stent thrombosis other than diabetes mellitus and stent thrombosis occurring during clopidogrel treatment.

- 4.12 The Committee considered the role of prasugrel in the treatment of patients with acute coronary syndromes taking proton pump inhibitors and was mindful of the statements provided by clinical specialists and NHS professionals in response to consultation. The Committee was also aware of European Medicines Agency (EMA) statements on the use of proton pump inhibitors in people taking clopidogrel that advise 'concomitant use of a proton pump inhibitor with clopidogrel is not recommended unless considered essential'. Although the Committee was aware that the SPC for prasugrel stated that proton pump inhibitors could be used with prasugrel and of statements received from the manufacturer during consultation that antiplatelet activity of prasugrel was not significantly affected by the use of a specific proton pump inhibitor, it was mindful that prasugrel had not been extensively studied with a range of proton pump inhibitors and that it may be too soon to dismiss similar co-prescribing concerns. The Committee concluded that, on balance, concomitant clopidogrel and proton pump inhibitor use was predominantly a prescribing issue and therefore it was most

appropriately addressed between the patient and their healthcare professional on an individual basis.

- 4.13 The Committee also discussed patients not included in the manufacturer's target population (patients aged 75 years or older and patients whose weight was below 60 kg). The Committee noted that a lower maintenance dose of 5 mg prasugrel was specified in the marketing authorisation for these patients, but that the evidence for treating these patients with prasugrel at the reduced dose in preference to clopidogrel was limited. The Committee agreed that the evidence was weak, but was not persuaded that the recommendations should differentiate between those included or not included in the target population.

Cost effectiveness

- 4.14 Bearing in mind its considerations on clinical effectiveness, the Committee, when considering the cost-effectiveness data, agreed that the advantage of prasugrel over clopidogrel was plausible in all patients with ST-segment-elevation MI and in all patients with diabetes mellitus (with ST-segment-elevation MI or non-ST-segment-elevation MI). However, the Committee considered that any advantage was highly uncertain in patients with non-ST-segment-elevation MI without diabetes.
- 4.15 The Committee first considered the estimates of cost effectiveness presented in the manufacturer's submission for the licensed population as a whole. It noted that the estimated QALY gains for prasugrel over the 40-year time horizon were small (in the region of 22 life-days, that is, 0.05 QALYs gained) and that the difference in cost between prasugrel treatment and clopidogrel treatment was also small over this timeframe. As a result, the cost effectiveness of prasugrel was highly susceptible to changes in key model assumptions. The Committee was mindful of the concerns

identified in considering the clinical evidence, the ERG's exploratory analysis and the manufacturer's own sensitivity analysis which was intended to compensate for the lack of clopidogrel preloading. The Committee agreed that the most plausible cost per QALY gained of prasugrel compared with clopidogrel would be much higher than presented in the manufacturer's base case. It noted that the exploratory analysis undertaken by the ERG increased the manufacturer's base-case ICER to more than £20,000 (without including an adjustment for the lack of preloading). Sensitivity analysis for clopidogrel preloading (conducted by the manufacturer) implied a further increase in the ICER of more than threefold from £6382 (no adjustment, original uncorrected model) to £22,727 (100% adjustment to account for lack of preloading with clopidogrel, that is equivalence between clopidogrel and prasugrel in the first 3 days). The Committee also considered the adjustments to the manufacturer model to reflect the ERG's exploratory analysis, but used the whole licensed population rather than the typical/median patient profile. The Committee agreed that the use of the whole licensed population for analysis was appropriate and that the utility values and underlying MI rates were plausible, but that the manufacturer's adjustments to mortality risk were not. Furthermore, the Committee noted its concern with regard to clinical effectiveness and the ERG's subgroup analyses in which the ICER for non-ST-segment-elevation MI patients without diabetes was over £130,000. The Committee therefore concluded that it could not recommend prasugrel for the whole population of patients for whom prasugrel is indicated in the marketing authorisation (or the target population), but agreed that cost-effectiveness analyses in subgroups of patients should be explored.

- 4.16 For patients with ST-segment-elevation MI, the Committee considered that no adjustment of the manufacturer's base case

was necessary to compensate for the lack of clopidogrel preloading, as the opportunity to preload would be limited for these patients. It further noted that the ICERs from the ERG's exploratory analyses in patients with ST-segment-elevation MI were £1805 per QALY gained for people with diabetes mellitus and £6616 per QALY gained for people without diabetes. Therefore prasugrel could be considered a cost-effective use of NHS resources and should be recommended as an option when immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary.

4.17 The Committee noted that patients with diabetes mellitus have a much greater risk of further cardiovascular complications or events than patients without diabetes. It also noted that the ERG's subgroup analyses reported an ICER for patients with diabetes and non-ST-segment-elevation MI of approximately £3000 per QALY gained. The Committee concluded that although this figure did not include the clopidogrel preloading adjustment (which increased the ICER in the manufacturer's sensitivity analyses for the non-ST-segment-elevation MI licensed population), the use of prasugrel for patients with diabetes undergoing percutaneous coronary intervention could be considered a cost-effective use of NHS resources and should be recommended as an option.

4.18 The Committee considered that patients in whom a stent thrombosis occurred during clopidogrel treatment could reasonably be considered at high risk of further cardiovascular events, they are clearly identified and they could potentially benefit from the option of treatment with an alternative such as prasugrel. It agreed that the use of prasugrel could reasonably be considered a more cost-effective option than continuing clopidogrel therapy in such patients. The Committee concluded that prasugrel could be considered a cost-effective use of NHS resources and that

prasugrel should be recommended as an option for the treatment of patients when a stent thrombosis has occurred during clopidogrel treatment.

4.19 For patients with non-ST-segment-elevation MI, but without diabetes, the Committee was mindful of concerns about the clinical evidence, particularly that the effectiveness of prasugrel was highly uncertain for these patients. Additionally, it noted that the ERG's subgroup analysis resulted in an ICER greater than £130,000 per QALY gained (with no adjustment for lack of clopidogrel preloading). The Committee therefore concluded that prasugrel would not be a cost-effective use of NHS resources in these circumstances and could not be recommended.

4.20 The Committee acknowledged that formulations of generic clopidogrel had received EMEA positive opinion in May 2009. It noted that the price of clopidogrel could change once generic formulations were made available. The Committee concluded that the guidance on prasugrel should be considered for review in 1 year's time when any substantial change to the nationally available price of clopidogrel could be considered.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Research, including clinical trials, analysis of registers and/or audit, into defining the risk factors for stent thrombosis and identifying groups who are at high risk of stent thrombosis while taking antiplatelet therapy should be performed.

7 Related NICE guidance

Published

- MI: secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/CG48
- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2004). Available from www.nice.org.uk/TA80
- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002). Available from www.nice.org.uk/TA47

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal guidance. Publication expected September 2010.
- Acute coronary syndromes: the management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline. Publication expected February 2010.

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in September 2010.

Andrew Stevens
Chair, Appraisal Committee
August 2009

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Kathryn Abel

Reader and Consultant Psychiatrist, University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Brian Buckley

Lay Member

Mr Mark Campbell

Director of Standards and Performance, NHS Bury

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Mr David Chandler

Lay Member

Dr Peter Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies

Consultant Physician, Royal Infirmary, Manchester

Mr Richard Deveraux Phillips

Public Affairs Manager, Medtronic

Professor Rachel Elliot

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Dyfrig Hughes

Senior Research Fellow, University of Wales Bangor

Professor Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Pro Vice Chancellor for Research & Enterprise, Keele University

Professor of Statistics, Keele University

Mr Henry Marsh

Consultant Neurosurgeon, St George's Hospital London

Professor Jonathan Michaels (Vice Chair)

Professor of Vascular Surgery, University of Sheffield

Professor Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Mrs Ruth Oliver-Williams

Head of Nursing, Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne

RCUK Senior Research Fellow in Health Economics, The University of Manchester

Dr Danielle Preedy

Lay Member

Dr Philip Rutledge

Consultant Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Andrew Stevens

Chair of Appraisal Committee C

Dr Matt Stevenson

Technical Director, School of Health and Related Research Technical Assessment Group, University of Sheffield

B ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Ruaraidh Hill, João Vieira

Technical Leads

Helen Chung

Technical Adviser

Laura Malone

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group, University of Liverpool:

- Greenhalgh J, Bagust A, Boland A, et al. Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: a single technology appraisal, April 2009.

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document. Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I and II also had the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Eli Lilly and Company (prasugrel)

II Professional/specialist and patient/carer groups:

- British Atherosclerosis Society
- British Cardiovascular Society
- British Geriatrics Society
- British Heart Foundation
- British Institute of Radiology
- Royal College of Nursing
- Royal College of Physicians
- Action Heart
- Heart Care Partnership

III Other consultees:

- Department of Health
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Sanofi-Aventis (clopidogrel)
- Bristol-Myers Squibb Pharmaceuticals (clopidogrel)
- Daiichi Sankyo
- National Institute for Health Research Health Technology Assessment Programme
- National Clinical Guidelines Centre for Acute and Chronic Conditions

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document.

- Dr Nick Curzen, nominated by The British Cardiovascular Society and The Royal College of Physicians – clinical specialist
- David Geldard, Immediate Past President, Heart Care Partnership (UK), nominated by Heart Care Partnership – patient expert
- Dr Tony Gershlick, consultant cardiologist, nominated by British Cardiovascular Society and The Royal College of Physicians – clinical specialist