Scottish Medicines Consortium

prasugrel 5 and 10mg tablets (Efient®) No. (562/09)
Daiichi-Sankyo/Eli Lilly and Company Limited

07 August 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

prasugrel (Efient®) co-administered with aspirin is accepted for restricted use within NHS Scotland for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention. Use is restricted to patients who are eligible to receive the 10mg dose of prasugrel.

When compared to an alternative antiplatelet agent, prasugrel demonstrated a significant reduction in the incidence of ischaemic events, mainly non-fatal myocardial infarction, in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Prasugrel was, however, also associated with an increased risk of clinically significant bleeding events.

Alternative treatments are available at a lower drug acquisition cost.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Co-administered with aspirin, for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

Dosing information

A single 60mg loading dose and then continued at 10mg daily, co-administered with aspirin (75 to 325mg daily). Patients weighing less than 60kg, should be given a 60mg loading dose but a reduced maintenance dose of 5mg daily. A treatment duration of up to 12 months is recommended, unless the discontinuation of prasugrel is clinically indicated.

Product availability date

27 March 2009

Summary of evidence on comparative efficacy

Prasugrel is an orally administered pro-drug which is metabolised *in vivo* to an active thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits platelet activation and aggregation.

The pivotal phase III study compared prasugrel with clopidogrel in 13,608 patients with acute coronary syndrome (ACS) who were scheduled to undergo percutaneous coronary intervention (PCI). Eligible patients had either (a) moderate to high risk unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) defined as ischaemic symptoms lasting ≥ 10 minutes occurring within 72 hours of randomisation, a Thrombosis In Myocardial Infarction (TIMI) risk score ≥ 3 and either segment deviation of ≥1mm or raised cardiac markers or (b) ST segment elevation myocardial infarction (STEMI) within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment for STEMI. Exclusion criteria of note included an increased risk of bleeding, anaemia, thrombocytopenia, a history of intracranial findings or the use of any thienopyridine within 5 days before enrolment. Patients were randomised to prasugrel or clopidogrel in a 1:1 ratio with stratification for clinical presentation. With the exception of patients presenting with STEMI with onset of symptoms < 12hours, all patients were randomised only after diagnostic angiography confirmed anatomy suitable for PCI. Prasugrel was administered as a 60mg loading dose followed by a 10mg daily maintenance dose and clopidogrel as a 300mg loading dose and a 75 mg daily maintenance dose for 6 to 15 months. All patients were also treated with aspirin (75 to 162mg daily). The loading dose of study drug was administered anytime between randomisation and one hour after leaving the catheterisation laboratory.

The primary efficacy endpoint was a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during the follow-up period. Secondary endpoints measured during the follow-up period included stent thrombosis and a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or rehospitalisation due to a cardiac ischaemic event.

Of the 13,608 patients enrolled, 10,074 had UA/NSTEMI and 3,534 STEMI. PCI at the time of randomisation was performed in 99% of patients and 94% received ≥1 stent. After a median follow-up of 14.5 months, the rate of the primary composite endpoint was 9.9% (643/6,813) in the prasugrel group compared with 12% (781/6,795) in the clopidogrel group, corresponding to a hazard ratio (HR) of 0.81 (95% confidence intervals (CI): 0.73 to 0.90). The difference between treatments also significantly favoured prasugrel at days 30 and 90. A significant reduction in the rate of the primary composite endpoint was achieved both in patients with UA/NSTEMI (9.9% versus 12% respectively; HR 0.82 [95%CI: 0.73 to 0.93]) and STEMI (10% versus 12% respectively; HR 0.79 [95% CI: 0.65 to 0.97]).

Of the composite endpoint, the only component to demonstrate a significant difference was the rate of non-fatal myocardial infarction which significantly favoured prasugrel (7.3% versus 9.5% respectively; HR 0.76 [95% CI: 0.67 to 0.85]). There were no significant differences between the treatment groups in the rate of cardiovascular death (2.1% versus 2.4% respectively; HR 0.89 [0.70 to 1.12]) or non-fatal stroke (1.0% versus 1.0% respectively; HR 1.02 [95% CI: 0.71 to 1.45]).

At follow-up, there were significant reductions in the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or rehospitalisation due to a cardiac ischaemic event in the prasugrel group compared to clopidogrel (12% versus 15% respectively) and in the rate of stent thrombosis (1.1% versus 2.4 respectively). The rate of urgent target vessel revascularistion was also significantly lower in the prasugrel group (2.5% versus 3.7% respectively).

Summary of evidence on comparative safety

The majority of drug related adverse events were related to bleeding and the risk was higher with prasugrel than with clopidogrel. Safety endpoints assessed during the pivotal study included TIMI major bleeding not related to coronary artery bypass grafting (CABG), non-CABG related TIMI life-threatening bleeding, CABG-related TIMI major bleeding and TIMI major or minor bleeding. Prasugrel was associated with an excess in TIMI major bleeding not related to CABG, 2.4% [146/6,741] versus 1.8% [111/6,716] in the clopidogrel group HR 1.32 [95% CI: 1.03 to 1.68]). This included a higher rate of life-threatening bleeding (1.4% versus 0.9% respectively HR: 1.52 [95% CI: 1.08 to 2.13]) and fatal bleeding (0.4% versus 0.1% respectively HR: 4.19 [95% CI: 1.58 to 11.11]). The incidence of CABG-related TIMI major bleeding was 13.4% in the prasugrel group and 3.2% in the clopidogrel group HR: 4.73 [95% CI: 1.90 to 11.82]. The incidence of TIMI major or minor bleeding was also significantly higher in the prasugrel group (5.0% versus 3.8% respectively).

Although the rate of bleeding was increased with prasugrel, analysis of net clinical benefit in the study population (defined as a composite of death from any cause, non-fatal myocardial infarction, non-fatal stroke and non-CABG related TIMI major bleeding) favoured prasugrel (12% versus 14%; HR 0.87 [95% CI: 0.79 to 0.95]). Post hoc analysis identified three groups of patients (aged ≥75 years, weighing <60kg or with a history of transient ischaemic attack (TIA) or stroke) who did not have a favourable net clinical benefit.

Treatment-emergent adverse events were reported in 80% of prasugrel and clopidogrel treated patients with a similar frequency of non-haemorrhagic adverse events in both groups (77% of prasugrel and 78% of clopidogrel patients). Coronary revascularisation, fatigue, myocardial infarction, constipation, musculoskeletal pain and cardiac failure were significantly more common in the clopidogrel group and pyrexia and tendency to bruise were significantly more common in the prasugrel group.

Serious adverse events occurred in 25% of prasugrel and 24% of clopidogrel patients with a similar incidence of non-haemorrhagic serious adverse events in each group (22% and 23% respectively) which most commonly were non-cardiac chest pain, coronary artery restenosis, chest pain and angina pectoris.

Summary of clinical effectiveness issues

In the pivotal study, prasugrel significantly reduced the incidence of ischaemic events as measured by the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared to clopidogrel. The difference between the two treatment groups was mainly driven by a difference in the incidence of myocardial infarction and there were no significant differences in cardiovascular death or non-fatal stroke. The incidences of urgent target vessel revascularisation and stent thrombosis were also significantly reduced by prasugrel.

However, these reductions have to be balanced against an increased incidence of bleeding, including major, life-threatening and fatal bleeding. In the pivotal study, post hoc analysis identified three groups of patients (aged ≥75 years, weighing <60kg or with a history of transient ischaemic attack (TIA) or stroke) at high risk of bleeding who did not have a favourable net clinical benefit. As a result, prasugrel is contraindicated in those with a history of TIA or stroke, generally not recommended in those aged ≥75 years and recommended at a lower maintenance dose in those weighing <60kg.

There was no mortality benefit associated with prasugrel and it is unclear how many symptomatic, clinical myocardial infarctions were reduced as these were not distinguished from those identified using biochemical markers only. However, retrospective classification of myocardial infarctions according to a classification system for the 'Universal Definition of Myocardial Infarction' showed that prasugrel significantly reduced the risk of myocardial infarctions that were procedure-related and non-procedure-related (mainly spontaneous), and those that were small and large, including new myocardial infarctions occurring during maintenance therapy.

Sub-group analysis found that the reduction in the primary composite endpoint was greater in patients with diabetes mellitus (12% of prasugrel patents and 17% of clopidogrel patients: HR 0.70 [95% CI: 0.58 to 0.85]) than without diabetes mellitus (9.2% and 11% respectively: HR 0.86 [95% CI: 0.76 to 0.98]) though the difference was significant in both sub-groups.

Although the comparator arm of the pivotal study used the licensed loading dose of clopidogrel (300mg), there is evidence to support the use of higher loading doses in practice. It is therefore unknown if the difference between prasugrel and a higher loading dose of clopidogrel would have reduced the difference between the groups. Duration of clopidogrel therapy was also longer than in current clinical practice (depending on the procedure, e.g. type of stent inserted). These factors may have influenced the bleeding rates associated with clopidogrel in the study.

Clinical guidelines currently recommend that the loading dose of antiplatelet is given immediately or before and not after diagnostic angiography as in the pivotal study. However the European Medicines Agency (EMEA) considered that there was sufficient evidence to suggest that this did not substantially affect the drugs' relative efficacies.

Bleeding risks vary according to the route used for PCI and details on the proportion of patients treated by the femoral or radial route are lacking.

Clopidogrel is licensed for other therapeutic indications including use for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral vascular disease. Clopidogrel (as hydrogen sulphate, Plavix®) is also licensed in combination with aspirin in non-ST elevation ACS including those undergoing PCI or in STEMI patients who are eligible for thrombolytic therapy.

Summary of comparative health economic evidence

The manufacturer conducted a cost-utility analysis in the form of a Markov model and extrapolation utilising individual patient data from the pivotal phase III study, in order to compare prasugrel (60mg loading dose and 10mg/day maintenance dose) plus aspirin with clopidogrel (300mg loading dose and 75mg/day maintenance dose) plus aspirin for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI. The comparator used was appropriate. The risk of primary cardiovascular (CV) events within the duration of the study was modelled using logistic and Weibull regressions. No additional treatment effect was assumed beyond the 12 month maximum duration of prasugrel or clopidogrel treatment although long run mortality was extrapolated through to a 40 year time horizon. The extrapolation involved an indirect assessment of the relative risk of mortality associated with non-fatal myocardial infarction/stroke events in the phase III study.

Analysis was performed for a number of patient groups. Although cost-effectiveness was assessed for all patients in the phase III clinical study (excluding those with prior stroke/TIA), the patient group of most relevance was those recommended to receive the 10mg maintenance dose of prasugrel, i.e. also excluding patients under 60kg and those aged ≥75 years. Using individual patient data, the estimated cost per QALY gained for this patient group was £3,779. This was based on an estimated incremental cost of £186 per patient, 0.06 life years and 0.05 QALYs gained per patient. There was a higher percentage of fatal bleeds (0.05% versus 0%) and major bleeds (1.95% versus 1.50%) in the prasugrel arm, but the adverse QALY impact of this was offset by fewer non-fatal myocardial infarctions (6.20% versus 8.15%) and marginally fewer CV deaths (1.36% versus 1.58%), with similar non-fatal strokes (0.58% versus 0.64%).

Analysis was also performed separately for UA/NSTEMI and STEMI patient sub-groups. The cost per QALY gained for the STEMI patient group was £2,421 (estimated incremental cost of £201, and life years gained of 0.11 and 0.08 QALYs per patient), and for the UA/NSTEMI patient group was £4,884 (estimated incremental cost of £181, and life years gained of 0.05 and 0.04 QALYs per patient). In both sub-groups prasugrel was associated with a reduction in non-fatal myocardial infarctions but higher risks of fatal/major bleeds than clopidogrel, the increase in bleeds was greatest for the UA/NSTEMI patients. The STEMI patient group also demonstrated reduced CV death but increased non-fatal stroke with prasugrel, although these results are uncertain.

Across patient sub-groups prasugrel was associated with a lower rate of re-hospitalisation due to CV events, revascularisations and bleeds. The methods of estimation of re-hospitalisation costs associated with CV events and bleeds appeared sufficiently robust. Disutility estimates for CV events were derived from a published study including ACS patients using the EQ 5D and adjusted for UK population norms and appeared plausible.

Probabilistic sensitivity analysis based on a single median patient profile, rather than the individual patient data, indicated a 68% probability of prasugrel being cost-effective at a £20,000 per QALY threshold, or approximately 70% at a threshold of £30,000 for the 10mg dose population, although the probability was higher (~87%) for the STEMI sub-group.

The predominant use of the median patient profile for one way sensitivity analysis for each sub-group, produced higher base cost/QALY results (e.g. £7,300 for the 10mg prasugrel dose target population), leading to some difficulty in interpretation.

There were, however, a number of concerns with the analysis, which if combined would suggest that the manufacturer's base case cost/QALY estimates were too optimistic, particularly for the UA/NSTEMI patient sub-group:

- The extrapolation to long run mortality outcomes was highly uncertain, and by the use of indirect relative risks of mortality from historical data (possibly based on clinical MIs alone), may have overestimated the long-term deaths prevented.
- The potential adverse impact on the cost/QALY assuming use of clopidogrel pre-loading was explored in scenario analysis and cost-effectiveness found to worsen in the UA/NSTEMI patient population.
- Clopidogrel duration of treatment in the trial was 12 months when in clinical practice shorter durations are likely (i.e. 3 months unless a drug eluting stent is used as confirmed by the clinical experts consulted). This would reduce the comparator costs with uncertain impact on relative effectiveness.

The manufacturer was therefore asked to provide some additional analysis to take account of these concerns. Analysis assuming the difference in treatment effect was reduced by 50% (to take account of clopidogrel pre-loading), a 0.5 mortality relative risk reduction and, for 65% of patients, only 3 months duration of clopidogrel treatment, resulted in an cost/QALY for the combined group of £11,262, £19,220 for the UA/NSTEMI group and £5,414 for the STEMI group. Given these estimates, the economic case was considered demonstrated.

Clinical experts have indicated a potential use for prasugrel in clopidogrel-resistant patients, however cost-effectiveness for this particular patient group has not been assessed.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Acute Coronary Syndromes, a national clinical guideline in February 2007. These guidelines predate the availability of prasugrel but recommend that patients with an ACS (in the presence of ischaemic ECG changes or elevation of cardiac markers) should be treated immediately with both aspirin (300mg) and clopidogrel (300mg); that clopidogrel should be continued for up to 4 weeks in patients with STEMI and for 3 months in patients with NSTEMI which may need to be extended to six months after drug-eluting stent implantation.

The European Society of Cardiology (ESC) published guidelines for PCI in 2005. These guidelines predate the availability of prasugrel but recommend that every patient scheduled for PCI should be considered for pre-treatment with clopidogrel initiated ≥6 hours before PCI with a loading dose of 300mg ideally administered the day before a planned PCI. If this is not possible a loading dose of 600mg should be administered ≥2 hours before PCI. Patients unable to be pre-treated with clopidogrel should receive the (possibly higher) loading dose immediately following the procedure.

The ESC published guidelines for the diagnosis and treatment of NSTE ACS in 2007. These guidelines predate the availability of prasugrel but recommend that all patients receive an immediate 300mg loading dose of clopidogrel followed by 75mg clopidogrel daily for 12 months unless there is an excessive risk of bleeding. In patients considered for an invasive procedure/PCI a loading dose of 600mg of clopidogrel may be used to achieve more rapid inhibition of platelet function.

The ESC published guidelines for the management of STEMI in 2008. These guidelines predate the availability of prasugrel but recommend an oral loading dose of ≥300mg of clopidogrel preferably 600mg to be administered as soon as possible to all STEMI patients undergoing PCI. A maintenance dose of clopidogrel 75mg daily should be continued for 12 months irrespective of acute treatment.

Additional information: comparators

The main comparator is clopidogrel.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Prasugrel	**60mg loading dose followed by 10mg daily**	**627**
Clopidogrel	300mg loading dose followed by 75mg daily	446

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 14 May 2009.

Additional information: budget impact

The manufacturer estimated a net drug budget impact for prasugrel of £79K in year 1 rising to £205K in year 5. The gross budget impact is estimated to be £271K in year 1 and £705K in year 5. This was based on a 14% uptake in year 1 (431 patients) and 35% (1,121) by year 5. Additional resource savings due to a reduction in hospitalisations were also estimated.

The net budget impact is likely to be an underestimate as it assumes that 12 months of clopidogrel would be displaced when shorter durations may be used in practice (3 months for a bare metal stent).

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 July 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15

European Medicines Agency (EMEA). European public assessment report (EPAR) for Drug prasugrel. www.emea.europa.eu