PUBLIC SUMMARY DOCUMENT
Product: Clopidogrel Hydrogen Sulfate, tablet 75 mg (base), Plavix®, Iscover®
Sponsor: Sanofi-Aventis Australia Pty Ltd, Bristol-Myers Squibb Pharmaceuticals.
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for the treatment of Acute Coronary Syndromes (ACS).

2. Background

At the June 1999 meeting, the PBAC recommended listing clopidogrel for the secondary prevention of ischaemic stroke and transient cerebral ischaemic events, and the secondary prevention of myocardial infarction or unstable angina in patients with a history of cerebrovascular ischaemic episodes while on therapy with low-dose aspirin, or where low-dose aspirin poses an unacceptable risk of gastrointestinal bleeding, or where there is a history of anaphylaxis, urticaria or asthma within four hours of ingestion of aspirin, other salicylates or NSAIDs. Listing was effective from 1 November 1999.

This was the first time the PBAC has considered clopidogrel for the treatment of ACS.

3. Registration Status

Clopidogrel was first registered by the TGA on 2 December 1998 and is marketed as Plavix and Iscover. Clopidogrel is indicated for:

- Prevention of vascular ischaemia associated with atherothrombotic events (myocardial infarction, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.
- Acute Coronary Syndrome. Clopidogrel is indicated in combination with aspirin for patients with the following:
    - Unstable angina or non-ST-elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). Clopidogrel is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent);
    - ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
Treatment of acute coronary syndromes (myocardial infarction or unstable angina) in combination with aspirin to prevent early and long-term atherothrombotic events.

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Acute Coronary Syndromes (ACS) covers a broad spectrum of clinical presentations including ST segment elevation myocardial infarction (STEMI), non-ST segment elevation

myocardial infarction (NSTEMI) and unstable angina (UA). STEMI and NSTEMI are types of heart attack that are differentiated by electrocardiogram (ECG). ACS is a set of signs and symptoms, usually a combination of chest pain and other features, interpreted as being the result of abruptly decreased blood flow to the heart (cardiac ischaemia); the most common cause for this is the disruption of an atherosclerotic plaque in a coronary artery.

The requested restriction would provide physicians with the option of initial dual antiplatelet treatment using clopidogrel in combination with aspirin.

6. Comparator

The submission nominated placebo as the main comparator. This is generally appropriate, however the PBAC considered a more accurate description of the comparison would be the comparison of aspirin plus clopidogrel versus aspirin alone in first-line secondary prevention in ACS.

7. Clinical Trials

The submission presented two direct randomised trials, CLARITY and CURE, comparing clopidogrel (loading dose 300 mg, maintenance 75 mg daily) plus aspirin (low dose) dual therapy with low dose aspirin therapy alone in patients with ACS as the scientific basis of the comparison. The CLARITY trial enrolled patients with ST-elevated myocardial infarction (STEMI) and the CURE trial enrolled patients with unstable angina and/or non ST-elevated myocardial infarction (UA/NSTEMI).

The details of these trials are presented in the table below.

Trial ID	Protocol title/Publication title	Publication citation
CURE (2001)	CURE – Clopidogrel in Unstable Angina to prevent Recurrent ischaemic Events (OASIS-4). Date: October 5, 2001.	Yusuf SZ. (2001). Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine; 345(7):494-502.**
CLARITY (2005)	CLARITY-TIMI 28- Clopidogrel as Adjuvant Reperfusion therapy- Thrombolysis in Myocardial Infarction-28. Date: October 3, 2005.	Sabatine MS et al. (2005) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. New England Journal of Medicine; 352(12):1179-1189.**

**other citations were found, but were not included as a reference with the submission.

The PBAC considered these trials to be the most relevant to the requested listing, as they provided a loading dose of clopidogrel 300 mg in accordance with current Australian practice guidelines.

8. Results of Trials

The results of CURE, conducted in patients with high risk UA/NSTEMI, are summarised in the table below. The first primary outcome was the first occurrence of any component of the composite cluster of death, from cardiovascular causes, non-fatal myocardial infarction or stroke. The second primary outcome was the first occurrence of any component of the composite cluster of the first primary outcome or refractory ischaemia.

Results of first and second co-primary outcomes of the CURE trial (up to 1 yr follow-up)

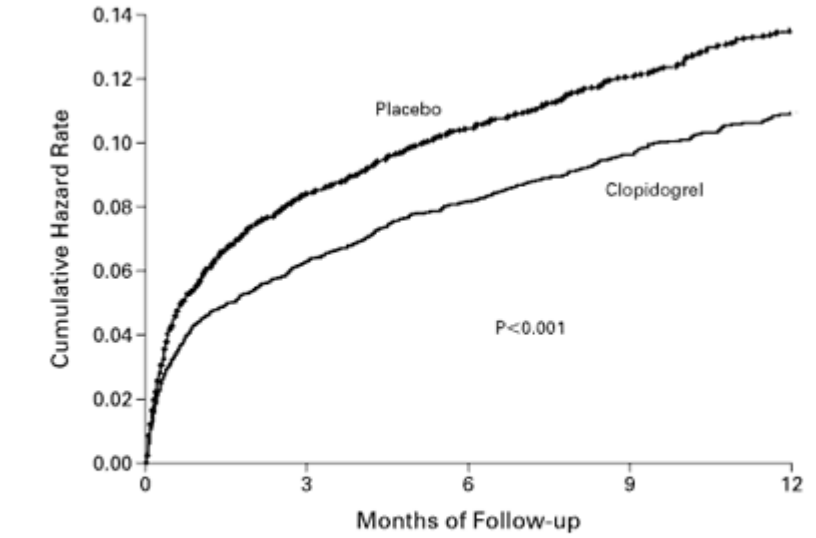
Co-primary outcomes	Clopidogrel n/N (%)	Placebo n/N (%)	Relative risk[a] (95% CI) p-value[b]
MI/Stroke/CV death[c]	582/6259 (9.3)	719/6303 (11.4)	**0.80 (0.72, 0.90) P<0.001**
MI/stroke/CV death/Refractory ischaemia	1035/6259 (16.5%)	1187/6303 (18.8%)	**0.86 (0.79, 0.94) P<0.001**

Abbreviations: CV=cardiovascular; MI=myocardial infarction; a= reported by the published report; b= log rank test; c= only the first event was counted.

The PBAC noted the primary outcome in the CURE trial occurred in 9.3 percent of patients in the clopidogrel group compared with 11.4 percent of patients in the placebo group, RR=0.80 (95% CI: 0.72-0.90; p<0.001).

The figure below shows the cumulative hazard rates over the 1-year duration of the CURE trial for the first co-primary outcome. The benefit of clopidogrel over placebo was evident early after randomisation and was maintained over the course of the study.

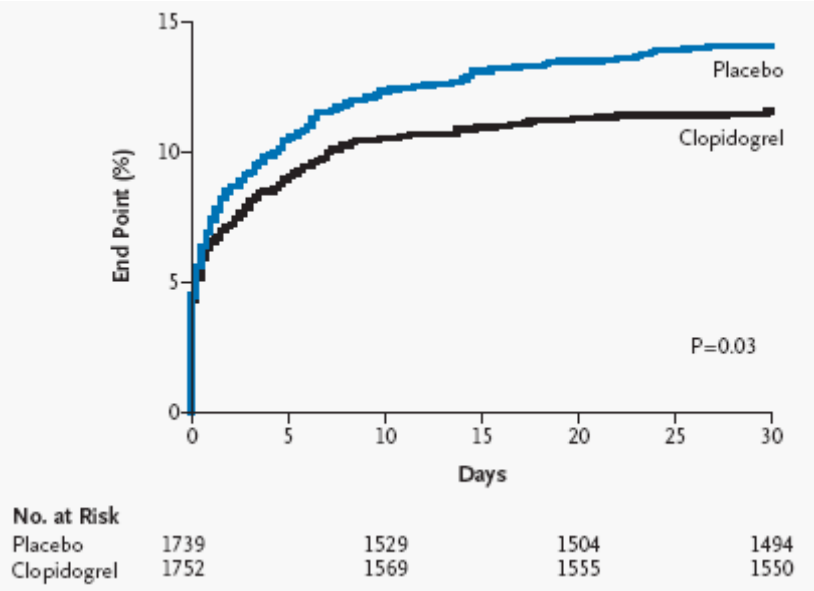
Cumulative hazard rates for the first co-primary outcome during the 12 months of study



The CLARITY trial of STEMI patients treated with fibrinolysis up to 30 days follow up found that treatment with clopidogrel was associated with a statistically significant 36% reduction in the odds of the primary outcome of occluded infarct-related artery on angiography or death or recurrent MI before angiography (OR: 0.64, 95% CIs 24%-47%, p<0.001) when compared to placebo.

The cumulative incidence for this composite endpoint is illustrated in the figure below.

Cumulative incidence for the composite endpoint of death, MI or myocardial ischaemia leading to revascularisation in the CLARITY trial at 30 days post-randomisation



Patients treated with clopidogrel/aspirin dual therapy are more likely to experience adverse events compared to treatment with aspirin alone, in particular, the risk of bleeding is increased with dual antiplatelet therapy. In the extended assessment of comparative harms, bleeding is also the most commonly reported adverse event.

In the CURE trial, after one year of follow up, there was significantly more major bleeding in the clopidogrel group than in the placebo group (3.7% vs. 2.7%; RR 1.38, 95% CI 1.13-1.67, p=0.001). There was no significant difference in the episodes of life-threatening bleeding (2.1% vs. 1.8%, p=0.13) or haemorrhagic strokes. The excess major bleeding episodes were mainly gastrointestinal bleeding. The risk of minor bleeding was significantly higher in the clopidogrel treated patients compared to those treated with placebo. In the CLARITY trial, patients were followed for 30 days and overall adverse events, treatment emergent severe adverse events, and adverse events leading to permanent discontinuations were similar between clopidogrel/aspirin treated and aspirin treated patients. In terms of summarising general safety, it appeared that after receiving treatment for one year (the CURE trial), patients treated with dual aspirin/clopidogrel experienced statistically more adverse events, whereas after receiving treatment for one month (30 days) the overall safety of clopidogrel/aspirin does not differ significantly from aspirin therapy alone.

In the CLARITY trial, the rate of the primary safety end point (thrombolysis in myocardial infarction (TIMI) defined major bleeding through the day after angiography) was 1.3% in the clopidogrel compared to 1.1% in the placebo group (p=0.64). At 30 days, there were no significant differences in the rates of major or minor bleeding between the two groups.

Overall, it appears from the results of CURE and CLARITY trials that the risk of bleeding is higher in clopidogrel plus aspirin treated patients compared to treatment with aspirin alone at one year and 30 days. In terms of absolute risk, the PBAC considered the increased risk of bleeding from dual anti-platelet therapy to be small.

The PBAC agreed that the trials demonstrated clopidogrel plus aspirin to be inferior to aspirin therapy alone in terms of comparative safety.

9. Clinical Claim

The submission described clopidogrel plus aspirin as superior in terms of comparative effectiveness and inferior in terms of comparative safety over aspirin therapy alone.

The PBAC accepted this claim.

10. Economic Analysis

The submission presented a modelled economic evaluation. The choice of the cost utility approach was valid. The submission conducted a cohort analysis of 1000 patients over a 10-year time horizon (base case). The resources included were drug costs, cost of cardiovascular events in ACS and cost of gastrointestinal bleeding as a result of side effect of antiplatelet therapy.

The incremental cost per extra MI/Stroke/Cardiovascular death prevented was estimated in the submission to be at the lower end of the range between $45,000 and $75,000. The incremental cost per LYG was estimated to be at the lower end of the range between $15,000 and $45,000, and the incremental cost per QALY was estimated to be less than $15,000.

Sensitivity analyses were conducted. The results were most sensitive to treatment effect applied in the modelled economic evaluation. When the upper 95% CI of relative risk for MI/stroke/CV death conferred by clopidogrel, the ICER of $/QALY increased to between $15,000 and $45,000. The submission assumed the one-year relative risks from the CURE trial apply in each year of the model. The PBAC acknowledged that major bleeding (defined as gastrointestinal bleeding in the model) outcomes do not significantly influence the ICER, nor does changes to assumptions regarding baseline CV death to non CV death ratios, nor variations in costs associated with the treatment groups.

The PBAC noted that there were some uncertainties associated with the modelling but that the sensitivity analyses had shown the ICERs to be robust.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be between 50,000 and 100,000 by Year 5 of listing, and the cost per year to the PBS to be between $60-100 million by Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of clopidogrel for the treatment of acute coronary syndromes in combination with aspirin based on an acceptable cost-effectiveness ratio compared to aspirin therapy alone. The submission calculated the incremental cost per extra QALY gained to be less than $15,000.

The PBAC considered the trials most relevant to the requested listing were CLARITY and CURE, both of which employed a loading dose of clopidogrel 300 mg in accordance with current Australian practice guidelines. The primary outcome in the CURE trial - a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke - occurred in 9.3 percent of the patients in the clopidogrel group and 11.4 percent of the patients in the

placebo group (relative risk (RR) with clopidogrel as compared with placebo, 0.80; 95 percent confidence interval (95% CI), 0.72 to 0.90; P<0.001). For the primary efficacy outcome of a composite of an occluded infarct related artery (IRA) on angiography, death or recurrent myocardial infarction by Day 8 or hospital discharge, with follow-up of 30 days, the CLARITY trial demonstrated treatment with clopidogrel was associated with a statistically significant 36% reduction in the odds of the outcome (OR: 0.64, 95% CI 24%-47%, p<0.001) when compared to placebo.

The PBAC noted patients treated with clopidogrel/aspirin dual therapy are more likely to experience adverse events compared to treatment with aspirin alone, in particular, the risk of bleeding is increased with dual antiplatelet therapy. In the extended assessment of comparative harms, bleeding was also the most commonly reported adverse event.

In the one year follow up of the CURE study, there were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs. 2.7% ;relative risk, 1.38; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 percent vs. 1.8 percent, P=0.13) or hemorrhagic strokes. The PBAC acknowledged that there is an increased risk of bleeding from dual antiplatelet therapy, however, in terms of absolute risk, this is small.

The PBAC agreed that the trials demonstrated that clopidogrel plus aspirin is superior in terms of comparative effectiveness and inferior in terms of comparative safety over aspirin therapy alone.

The PBAC noted there were some uncertainties associated with the modelling but that the sensitivity analyses had shown the incremental cost-effectiveness ratios (ICER) to be robust. Major gastrointestinal bleeding outcomes do not significantly influence the ICER, nor does changes to assumptions regarding baseline cardiovascular (CV) death to non CV death ratios, nor variations in costs associated with the treatment groups.

The PBAC considered duration of treatment was a clinical decision, and requested that the National Prescribing Service provide information on the potential for rebound, and the need to manage dose reduction. The PBAC also supported the QUM activities proposed in the Pre-PBAC response.

Lastly, the Committee noted that not all appropriate clinical use of clopidogrel may be covered by the current restriction applying to its PBS listing. The use of clopidogrel following coronary artery stenting procedures is of most interest. This indication is not PBS subsidised unless the patient undergoing stenting qualifies through one of the current PBS listing restrictions, but preliminary clinical advice indicates that anti-blood clotting therapy (using both clopidogrel and aspirin) is a long-term requirement following stenting procedures to prevent blood clots reforming later. It is likely that some patients with stents may not access PBS subsidised prescriptions, creating an inequitable arrangement whereby some patients pay the full cost of a necessary treatment whilst others do not. The PBAC requested the Department initiate a cost effectiveness review of clopidogrel with the objective of finding the best clinical place of clopidogrel as supported by evidence of efficacy, safety and cost effectiveness, and to ensure that the PBS indications reflect this use.

The sponsors should be invited to provide any information they might like to contribute towards this review, in due course.

Recommendation

CLOPIDOGREL HYDROGEN SULFATE, tablet, 75 mg (base).
Extend listing to include:

Restriction:	Authority required (STREAMLINED) Treatment of acute coronary syndromes (myocardial infarction or unstable angina) in combination with aspirin to prevent early and long-term atherothrombotic events.
Maximum quantity:	28
Repeats:	5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The co-sponsors are pleased that patients will have more affordable access to this lifesaving medicine which is estimated to prevent around 12,500 events over five years compared to the current PBS listing. The co-sponsors will work with the Department to expedite the review of clopidogrel in coronary artery stenting to ensure equitable access for all stented patients.