PUBLIC SUMMARY DOCUMENT
Product: TICAGRELOR, tablet, 90 mg, Brilinta®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for treatment of acute coronary syndromes (ACS) (myocardial infarction (MI) or unstable angina) in combination with aspirin.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Ticagrelor was TGA registered on 21 June 2011 for use in combination with aspirin, for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Treatment of acute coronary syndromes (myocardial infarction or unstable angina) in combination with aspirin.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Acute coronary syndrome is a term used to describe the symptoms of coronary artery disease, which include unstable angina, non-ST elevation MI and ST-elevation MI. Acute coronary syndrome is associated with atherosclerosis (build up of cholesterol-laden plaques) and is usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in coronary blood flow.

Platelets play a central role in the pathogenesis of atherothrombosis and the formation of thrombi following percutaneous coronary intervention (with or without stenting). Activated platelets are recruited to sites of coronary plaque rupture and intra-arterial stenting, thereby forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and MI.

When oral anti-platelet therapy is indicated, ticagrelor is proposed as an alternative treatment option to existing agents.

6. Comparator

The submission appropriately nominated clopidogrel as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one head-to-head randomised trial (PLATO) comparing ticagrelor with a loading dose of 180 mg to 270 mg and a maintenance dose of 90 mg twice daily with clopidogrel with a loading dose of 300 mg to 600 mg and a maintenance dose of 75 mg/day (both used in combination with aspirin) in patients with acute coronary syndromes (myocardial infarction or unstable angina). Publication details of the PLATO trial as presented in the submission are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
PLATO		
Wallentin L, et al	Ticagrelor versus clopidogrel in patients with acute coronary syndromes	*N Eng J Med* 2009; 361(11): 1045-1057
Cannon CP, et al	Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study	*The Lancet* 2010; 375: 283-293
James S, et al	Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial.	*Am. Heart J.* 2009; 157(4): 599-605
Storey RF, et al	Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes.	*J. Am. Coll. Card.* 2010; 56: 1456-1462
Wallentin L, et al	Effect of CYP2C19 and ABCB1 singe nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial	*The Lancet* 2010; 376: 1320-1328
Montalescot G, Silvain J.	Ticagrelor in the renal dysfunction subgroup: Subjugated or substantiated?	*Circulation* 2010; 122(11): 1049-1052.
Kleiman NS.	PLATO study of ticagrelor versus clopidogrel in patients with high-risk acute coronary syndromes.	*Curr. Cardiol. Rep.* 2010; 12(4): 283-285.
Husted S, et al	Changes in inflammatory biomarkers in patients treated with ticagrelor or clopidogrel.	*Clin. Cardiol.* 2010; 33(4): 206-212.
James S, et al	Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: Results from the platelet inhibition and patient outcomes (PLATO) trial.	*Circulation* 2010; 122(11): 1056-1067.

8. Results of Trials

The table and figure below summarise the results of the primary outcome of the PLATO trial – a composite of vascular death, MI (excluding silent MI) and stroke.

Results of primary outcomes of the PLATO trial (up to 12 months follow up)

Endpoint	Ticagrelor N=9,333 n (%)	Clopidogrel N=9,291 n (%)	HR (95% CI)	P-value
Composite of vascular death/MI (excluding silent MI)/Stroke	864 (9.3)	1,014 (10.9)	**0.84 (0.77, 0.92)**	**0.0003**

Bolded typography indicates statistically significant differences between treatment groups

For the primary endpoint in the PLATO trial, a statistically significant difference between treatments was observed favouring ticagrelor (Hazard Ratio: 0.84 [95% CI: 0.77, 0.92]), although it was noted that the difference in stroke events was not statistically significant.

The submission performed exploratory analyses by sub-groups to assess consistency of treatment effect for the primary efficacy endpoint. In analyses of the 31 predefined subgroups, overall the benefit of ticagrelor over clopidogrel was found to be consistent. The observed benefit of ticagrelor appears to be reduced in patients weighing less than the median weight for their sex, patients not taking lipid-lowering drugs at randomisation and patients enrolled in North America. (which represented approximately 10% of the overall population studied). This may well represent a simple artefact of retrospective subgroup analysis in only about 10% of the total enrolment. However, it was noted that half of US patients received an aspirin maintenance dose of 325 mg, whereas the majority of non-US patients received 75 or 100 mg. Higher maintenance-doses of aspirin were associated with relatively unfavourable outcomes with ticagrelor. Following consideration of this and other possible explanations contained within a US FDA discussion paper on the issue, the PBAC was reassured of ticagrelor's comparative benefits over clopidogrel.

For PBAC's comments on these results, see Recommendation and Reasons.

The table below summarises the main adverse events in the PLATO trial (up to 12 months follow up).

Summary of the main adverse events in the PLATO trial (up to 12 months follow up)

Endpoint	Ticagrelor N=9,235 n (%)	Clopidogrel N=9,186 n (%)	HR (95% CI)	P-value
Primary Safety Endpoint (PLATO defined)				
Total major bleeding	961 (10.4)	929 (10.1)	1.04 (0.95, 1.13)	0.4336
Secondary Safety Endpoints – Total major bleeding by severity (PLATO defined)				
Major fatal/life-threatening	491 (5.3)	480 (5.2)	1.03 (0.9, 1.16)	0.6988
Fatal	20 (0.2)	23 (0.3)	0.87 (0.48, 1.59)	0.6553
Life-threatening[a]	471 (5.1)	459 (5.0)	-	-
Major other[a]	494 (5.3)	474 (5.2)	-	-
Major Bleeding				
CABG related (all patients) PLATO defined 'Major' bleeding events and similar TIMI-defined bleeding events				
PLATO-defined major	619 (6.7)	654 (7.1)	0.95 (0.85, 1.06)	0.32
TIMI-defined major	657 (7.1)	638 (6.9)	1.03 (0.93, 1.15)	0.5669
TIMI-defined major + minor	946 (10.2)	906 (9.9)	1.05 (0.96, 1.15)	0.3272
Non-CABG related PLATO defined 'Major' bleeding events and similar TIMI-defined bleeding events				
Total major bleeding (PLATO defined)	362 (3.9)	306 (3.3)	**1.19 (1.02, 1.38)**	**0.0264**
Major fatal/life-threatening (PLATO	171 (1.9)	151 (1.6)	1.14 (0.91, 1.41)	0.2516

defined)				
TIMI-defined major bleeding	221 (2.4)	177 (1.9)	**1.25 (1.03, 1.53)**	**0.0246**
TIMI-defined major + minor	360 (3.9)	295 (3.2)	**1.23 (1.05, 1.43)**	**0.0093**
PLATO-defined 'Combined major + minor bleeding events	1,339 (16.1)	1,215 (14.6)	**1.11 (1.03, 1.2)**	**0.0084**
Non-procedural bleeding events by severity (PLATO defined)				
Combined major + minor[b]	457 (4.9)	332 (3.6)	**1.39 (1.21, 1.60)**	**<0.0001**
Major	235 (2.5)	180 (2.0)	**1.31 (1.08, 1.60)**	**0.0058**
Fatal/life Threatening	103 (1.1)	95 (1.0)	1.09 (0.82, 1.44)	0.5456
Fatal[c]	13 (0.1)	12 (0.1)	1.09 (0.50, 2.38)	0.8331
Minor bleeding				
Minor bleeding study criteria	442 (4.8)	349 (3.8)	**1.26 (1.10, 1.45)**	**<0.05**
Minor bleeding - non procedural related	237 (2.6)	161 (1.8)	**1.46 (1.20, 1.79)**	**<0.05**
General AEs (including bleeding events)				
Any AE	6,714 (72.7)	6,398 (69.6**)**	-	-
Mild	5,655 (61.2)	5,292 (57.6)	-	-
Moderate	3,322 (36.0)	3,073 (33.5)	-	-
Severe	1,019 (11.0)	1,061 (11.6)	-	-
Any SAE	1,864 (20.2)	1,866 (20.3)	-	-
SAE excluding death	1,712 (18.5)	1,685 (18.3)	-	-
Death	218 (2.4)	285 (3.1)	-	-
Leading to study drug discont	687 (7.4)	500 (5.4)	-	-
SAE	259 (2.8)	218 (2.4)	-	-
Dyspnoea[d]	1,270 (13.8)	721 (7.8)	-	-

[a] time to first event is not calculated for 'life-threatening' and 'major other' bleeding because it may be proceeded by a more severe bleed. Patients may be counted in >1 bleeding event category.

[b] patients may be counted in >1 bleeding event category

[c] >1 fatal bleeding event was ICAC-adjudicated for 1 patient in the clopidogrel group

[d] patients with at least 1 event, Source: Table 68, p270 of the PLATO trial report, OR (95% CI)=1.84 (1.68, 2.02) Wallentin et al (2009)

n= patients with adverse events, TIMI=Thrombolysis in Myocardial Infarction, discont=discontinuation

Patients treated with ticagrelor were observed to have an increase in non-CABG related PLATO defined 'Major' bleeding events and similar Thrombolysis in Myocardial Infarction (TIMI)-defined bleeding events, non-procedural bleeding events by severity (PLATO defined), minor bleeding and dyspnoea. Ticagrelor was not associated with a significant increase in total major or fatal/life-threatening bleeds.

The PBAC also noted the special report from the FDA on ticagrelor (Gaglia, M. & Waksman, R. 'Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee Meeting Regarding Ticagrelor', *Circulation* 2011; 123: 451). Some of the key findings from this report included:

- The sponsor estimated that 9 in 1000 patients would discontinue ticagrelor because of dyspnoea. Data was also presented showing that patients with cardiopulmonary disease at baseline did not have an increased relative risk of dyspnoea. Furthermore, patients taking ticagrelor did not have measurable changes in pulmonary function.
- Patients taking ticagrelor versus clopidogrel had more ventricular pauses ≥3 seconds on Holter monitoring during the first week of treatment (5.8% versus 3.6%; P = 0.01). These pauses, however, did not result in an increase of other arrhythmias or need for pacemaker insertion. Furthermore, the benefit of ticagrelor with regard to the primary end point was maintained in patients with pauses.

The PBAC considered that these were not major concerns.

9. Clinical Claim

The submission described ticagrelor as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over clopidogrel in combination with aspirin. Based on the supporting data, the PBAC considered this description was reasonable for the claim regarding comparative effectiveness, but the claim regarding comparative safety may not be reasonable. *For further details of PBAC's view, see Recommendation and reasons.*

10. Economic Analysis

A stepped economic evaluation was presented. The model consisted of five health states: event-free, MI, stroke, CV death and other death. Patients in the model were based on those in the PLATO trial (average age of 62 years, 29% women); they had had an ACS event and entered the model in the event-free state. In the first year, the model has 4 cycles of varying length. Patients transit from the event-free health state to the other health states by transition probabilities derived for the specified time periods from patient-level data from the PLATO trial. The model appropriately also included adverse events (non-CABG major bleed, minor bleeds and dyspnoea). For the remaining 9 years of the time horizon, the model has annual cycles.

The base case of the modelled economic evaluation assumed that the duration of treatment were 246 days for ticagrelor and 250 days for clopidogrel (derived from the PLATO trial) for an estimated 9 packs of each therapy over 12 months. In addition, the submission assumed that for the treatment duration patients adherence (defined as taking ≥80% of medication) was 83% in both treatment groups. The requested restriction for ticagrelor does not specify duration of treatment and it is implied to be life-long.

The base case incremental cost per quality adjusted life year (QALY) gained was less than $15,000.

The ICER was sensitive to assumptions regarding the costs for the index ACS event and assumptions regarding treatment duration and compliance.

Sensitivity analyses presented by the sponsor to address the uncertainty regarding duration of treatment produced an ICER of between $15,000 and $45,000 when a continued treatment costs for 4 years and a constant treatment effect based on the combined event rate from the last period of the trial are assumed.

For PBAC's view, see Recommendation and Reasons.

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 in Year 5, at an estimated net cost to the PBS of between $50 and $100 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of ticagrelor 90 mg as an Authority Required (Streamlined) benefit for the treatment of acute coronary syndrome (myocardial infarction or

unstable angina) in combination with aspirin on the basis of acceptable cost-effectiveness compared with clopidogrel in combination with aspirin.

Given that the submission was based on clinical efficacy data up to 12 months and the fact that clinical guidelines recommend therapy for up to 12 months in the treatment of ACS, the PBAC considered whether it would be appropriate for the restriction to limit treatment up to a maximum of 12 months duration. However, the PBAC considered that length of treatment should be determined by the treating clinician and noted that the restrictions for similar drugs, clopidogrel and prasugrel, do not define treatment duration despite the listing of these drugs also being based on trials that limited treatment duration.

The PBAC accepted the Restriction Working Group's advice that 'acute coronary syndrome' in place of 'acute coronary syndromes' better describes the PBS-eligible population and that such wording should also flow onto the current PBS restrictions for clopidogrel and clopidogrel with aspirin.

The submission's nominated comparator, clopidogrel, was considered appropriate by the PBAC. Consideration of prasugrel as a relevant comparator was discussed by the PBAC but it was noted that between clopidogrel and prasugrel as antithrombotic agents, clopidogrel currently has the majority of use in clinical practice and has a restriction which is the same as the requested restriction for ticagrelor. Also, it was noted that unlike clopidogrel, prasugrel is only available for a subgroup of ACS patients (i.e. those with ACS managed by PCI).

The PBAC considered that the results of the PLATO trial presented in the submission support the claim of superior comparative effectiveness of ticagrelor over clopidogrel. For the primary endpoint in the PLATO trial which was a composite of cardiovascular death, MI (excluding silent MI) and stroke up to 12 months of follow up, a statistically significant difference between treatments was observed favouring ticagrelor (Hazard Ratio: 0.84, 95% CI: 0.77, 0.92), although it was noted that the difference in stroke events was not statistically significant.

The PBAC noted clinical efficacy data that suggested that ticagrelor is less effective than clopidogrel in terms of reducing the number of ACS events in North American patients. This may well represent a simple artefact of retrospective subgroup analysis in only about 10% of the total enrolment. However, it was noted that half of US patients received an aspirin maintenance dose of 325 mg, whereas the majority of non-US patients received 75 or 100 mg. Higher maintenance-doses of aspirin were associated with relatively unfavourable outcomes with ticagrelor. Following consideration of this and other possible explanations contained within a US FDA discussion paper on the issue, the PBAC was reassured of ticagrelor's comparative benefits over clopidogrel.

The PBAC considered the submission's claim of comparable safety to clopidogrel may not be reasonable. It was noted that patients treated with ticagrelor were observed to have an increase in non-CABG related PLATO defined 'Major' bleeding events (Hazard Ratio: 1.04, 95% CI: 0.95, 1.13) ($p<0.4436$) and similar TIMI-defined bleeding events, non-procedural bleeding events by severity (PLATO defined), minor bleeding and dyspnoea. The PBAC further noted a lack of long term safety data beyond 12 months and FDA reports of discontinuations because of dyspnoea and ventricular pauses. However, with respect to dyspnoea and ventricular pauses, these were not major concerns for the PBAC.

A stepped economic evaluation was presented through a cost-utility analysis and a cost-effectiveness analysis (estimating the incremental cost per events avoided from 'within' the PLATO trial and life-years-gained). The PBAC considered the submission's ICER of less than $15,000 per QALY gained to be acceptable. The PBAC noted that the economic model was most sensitive to duration of treatment and that the modelled economic evaluation assumed duration of treatment to be one year. However, the PBAC noted that the requested listing did not limit treatment to one year and considered that in reality, it is likely that treatment will continue beyond one year in some patients.

To address the uncertainty regarding duration of treatment, in its pre-PBAC response, the sponsor presented a sensitivity analyses based on an extended duration of treatment and constant treatment effect. In the most extreme case, assuming continued treatment costs for 4 years and a constant treatment effect based on the combined event rate from the last period of the trial, the ICER increased to between $15,000 and $45,000 per QALY gained. The PBAC considered this revised ICER to still represent acceptable cost effectiveness.

The PBAC considered the submission's estimates on ticagrelor PBS usage and financial implications to be uncertain due to the high potential for ticagrelor to be used in non-ACS conditions by clinicians. On the other hand, may be less than predicted due to adverse events associated with ticagrelor (e.g. increased non-CABG bleeding) and potentially lower compliance arising from a twice daily dosing schedule compared to clopidogrel's once daily dosing. The high potential for ticagrelor to be prescribed for non-ACS conditions was of particular concern to the PBAC as use in such conditions has the potential to result in high costs to the PBS. To address the issue of ticagrelor's potential use outside any PBS restriction, the PBAC recommended that the Department enter into a risk share agreement with the sponsor.

The PBAC recommended that ticagrelor be included in the PBS medicines for prescribing by nurse practitioners within a shared care model.

Recommendation:
TICAGRELOR, tablet, 90mg

Restriction:	Authority Required (STREAMLINED) Treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin.
Maximum Quantity	56
No. of 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 sponsor had no comment