

**5.15 PRASUGREL,
Tablet 5 mg,
Tablet 10 mg,
Prasugrel SCP,
GENERIC HEALTH PTY LTD.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for prasugrel, in combination with aspirin, for the treatment of acute coronary syndrome (ACS) i.e., myocardial infarction or unstable angina, managed by percutaneous coronary intervention (PCI).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus ticagrelor, in combination with aspirin.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adults with acute coronary syndrome (MI or UA) managed by PCI, in combination with aspirin
Intervention	Prasugrel 60 mg (loading dose) then 10 mg/day (maintenance dose), or 5 mg/day maintenance dose if aged ≥75 years or weight <60 kg, with concomitant aspirin at 75 mg – 325 mg/day
Comparator	Primary comparator: ticagrelor 180 mg (loading dose) then 90 mg twice daily (maintenance dose), with concomitant aspirin at 75 mg – 150 mg/day Secondary comparator: clopidogrel 300 mg (loading dose) then 75 mg/day (maintenance dose), with concomitant aspirin at 75 mg – 325 mg/day
Outcomes	Composite of death, MI or stroke; mortality (all cause), stroke, MI, stent thrombosis, bleeding.
Clinical claim	Prasugrel with aspirin is superior in terms of effectiveness and non-inferior in terms of safety compared to ticagrelor with aspirin. No clinical claim was made for the comparison with clopidogrel, with the submission stating that the PBAC previously accepted that the superior comparative clinical benefit of prasugrel over clopidogrel, in terms of reduced non-fatal MI events, marginally outweighed the inferior comparative safety profile in terms of a higher incidence of adverse bleeding events (Section 12, Prasugrel PSD, July 2009 PBAC meeting).

Source: Table 1-1, p14 of the submission.

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; PSD, Public Summary Document; UA, unstable angina

2 Background

Registration status

- 2.1 Prasugrel SCP was listed on the Australian Register of Therapeutic Goods on 26 June 2020 for the following indication, when co-administered with aspirin:

The prevention of atherothrombotic events (myocardial infarction, stroke and cardiovascular death) in patients with acute coronary syndromes (moderate to high-risk unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI)) who are to undergo percutaneous coronary intervention (PCI).

- 2.2 The approved registration was based on a generic medicine application compared to the Effient® brand of prasugrel. The approved registration stated that the generic prasugrel tablets could be considered bioequivalent to Effient prasugrel film-coated tablets.

Previous PBAC consideration

- 2.3 Prasugrel (Effient) was PBS-listed on 1 December 2009 for the treatment of ACS managed by PCI in combination with aspirin, on the basis of superior comparative clinical benefit of prasugrel over clopidogrel (reduced non-fatal myocardial infarction events), which marginally outweighed the inferior comparative safety profile (higher incidence of adverse bleeding events; Section 12, Prasugrel Public Summary Document (PSD), July 2009 PBAC meeting).
- 2.4 Prasugrel was PBS-listed until 1 July 2020 when the brand and product was delisted from the PBS. NPS MedicineWise RADAR (17 May 2022) reported that prasugrel experienced lower uptake in clinical practice than other available P2Y12 inhibitors, potentially due to factors such as higher bleeding risk (compared to clopidogrel) and inability to use outside patients receiving PCI¹. Since this time, prasugrel has not been available on the PBS.
- 2.5 Ticagrelor was PBS-listed on 1 August 2012 on the basis of acceptable cost-effectiveness compared with clopidogrel in combination with aspirin. Consideration of prasugrel as a relevant comparator was discussed by the PBAC but it was noted that clopidogrel had the majority of use in clinical practice, as well as the same restriction as the requested restriction for ticagrelor. It was noted that prasugrel was only available for a subgroup of ACS patients (i.e. those with ACS managed by PCI).
- 2.6 The PBAC has not previously considered the comparison of prasugrel and ticagrelor treatment.
- 2.7 Table 2 below outlines the prices of clopidogrel, clopidogrel with aspirin, prasugrel and ticagrelor on the PBS over time. The ESC noted that the proposed price of prasugrel was higher than when it was delisted in July 2020, while the price of clopidogrel was substantially lower than when prasugrel was listed for ACS.

¹ <https://www.nps.org.au/radar/articles/clopidogrel-and-clopidogrel-with-aspirin-now-unrestricted-on-pbs>

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Table 2: DPMQs for clopidogrel, clopidogrel with aspirin, prasugrel and ticagrelor over time

PBS Schedule; event	Clopidogrel 75 mg, 28	Clopidogrel 75 mg with aspirin 100 mg, 30	Prasugrel 5 mg, 28 10 mg, 28	Ticagrelor 90 mg, 56
November 1999: Clopidogrel listed for secondary prevention of stroke, MI	\$83.77	-	-	-
February 2009: Clopidogrel listed for ACS	\$80.49	-	-	-
August 2009: Clopidogrel listed for stent insertion	\$80.92	-	-	-
December 2009: Clopidogrel with aspirin listed; prasugrel listed for ACS	\$80.92	\$86.25	\$96.43 \$106.43	-
August 2012: Ticagrelor listed for ACS	\$50.15	\$74.97	\$96.53 \$106.53	\$149.10
June 2020: Prior to prasugrel being delisted in July 2020	\$15.57	\$15.86	\$81.44 \$89.22	\$134.61
May 2022: Clopidogrel and clopidogrel plus aspirin unrestricted listing	\$16.29	\$16.56	-	\$136.37
December 2023: Current (proposed) prices	\$17.08	\$17.37	Proposed \$ \$	\$130.81

Source: Relevant PBS Schedules

Abbreviations: ACS, acute coronary syndrome; DPMQ, dispensed price for maximum quantity; MI, myocardial infarction; PBS, Pharmaceutical Benefits Scheme

Note: Clopidogrel, clopidogrel with aspirin and ticagrelor are eligible for 60-day dispensing (clopidogrel 75 mg, 56: \$21.17; clopidogrel 75 mg with aspirin 100 mg, 60: \$21.75; ticagrelor 90 mg, 112: \$253.63; December 2023 PBS Schedule).

For more detail on PBAC's view, see Section 7 PBAC outcome.

3 Requested listing

3.1 The proposed restriction is presented below. Secretariat additions are in italics and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PRASUGREL					
prasugrel 5 mg tablet, 28	\$	1	28	5	Prasugrel SCP
prasugrel 10 mg tablet, 28	\$	1	28	5	Prasugrel SCP
Restriction Summary [new] /TOC [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]					
Administrative Advice: <i>Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>					
Indication: Acute coronary syndrome (myocardial infarction or unstable angina)					
Treatment Phase: [blank]					
Clinical criteria: The treatment must be in combination with aspirin					
AND					
Treatment criteria-Clinical criteria					
Patient must have percutaneous coronary intervention planned, OR					

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Patient must have previously undergone percutaneous coronary intervention or previously have had percutaneous coronary intervention planned;
AND
Clinical criteria
Patient must not have a known history of <i>either (i) stroke or (ii) transient ischaemic attack.</i>
Population criteria:
Patient must be aged 18 years or older. <i>Patient must be at least 18 years of age.</i>
Prescribing Instructions: Patients aged over 75 years, or patients weighing less than 60 kg, are recommended to use a 5 mg/day maintenance dose.

- 3.2 The maximum quantity and number of repeats are consistent with the listings for ticagrelor and clopidogrel; however, 60-day prescribing is also available for ticagrelor, clopidogrel, and clopidogrel with aspirin.
- 3.3 The requested restriction for prasugrel was proposed to be consistent with the current PBS listing for ticagrelor. However, three additional criteria were proposed for the prasugrel restriction in order to align it with the prasugrel Product information and the clinical trial evidence: (i) patients must be 18 years or older, (ii) have no known history of stroke or transient ischaemic attack (TIA), and (iii) must have undergone PCI or have a PCI planned. To be consistent with the clinical trial evidence the recommended age for the lower maintenance dose should be for patients aged ≥ 75 years and not > 75 years. Ticagrelor does not have a reduced dose for older or lower-weight patients.
- 3.4 The requested restriction for prasugrel is narrower than for clopidogrel, which has an unrestricted listing.
- 3.5 The requested restriction is narrower than the TGA indication, as patients must be 18 years of age or older and must not have a known history of stroke or transient ischaemic attack. The TGA indication specifies that treatment is for patients with moderate to high-risk unstable angina (UA), NSTEMI or STEMI who are to undergo PCI, while the requested restriction allows for patients who have a planned or previous PCI, or who had PCI planned previously. The submission stated that this criterion is worded as such to allow patients who initially received prasugrel due to being indicated for PCI, but who did not ultimately go on to receive the PCI, to be eligible to continue prasugrel treatment without requiring any separate continuing treatment restrictions to be met. The ESC considered that use of prasugrel should be ceased if a patient does not undergo a PCI, noting that this was consistent with the clinical trial data and the registered TGA indication.
- 3.6 The submission noted that the Australian Therapeutic Guidelines (2023) recommend dual antiplatelet therapy for at least 12 months following an ACS (other than for a subset of patients at increased risk of bleeding), and for longer than 12 months in patients at high risk of recurrent ischaemic events. The sponsor argued that it is reasonable to assume a large component of the target population in the submission could be considered patients at a high risk of recurrent ischaemic events, and as such, continuation criteria for prasugrel are not required as patients can be expected to

continue on treatment to reduce the ongoing risk of ACS events, rather than demonstrate a level of response to treatment. The submission noted that the current PBS listings for ticagrelor and clopidogrel do not include continuation criteria, and that the PBAC has previously considered that the length of treatment for prasugrel, ticagrelor and clopidogrel should be determined by the treating clinician rather than limit treatment up to a maximum of 12 months duration (Ticagrelor analysis of predicted versus actual utilisation, DUSC report, February 2016). While the extent of use of prasugrel beyond 12 months is unclear, the lack of continuation criteria in the requested restriction was reasonable. The Australian Therapeutic Guidelines (2023) state that the typical treatment duration with P2Y12 inhibitors is 12 months. The 2016 DUSC analysis of predicted versus actual utilisation of ticagrelor noted that although some patients remained on treatment for more than two years, approximately 50% stopped taking ticagrelor one year after initiation (2016 Ticagrelor DUSC analysis).

For more detail on PBAC's view, see Section 7 PBAC outcome.

4 Population and disease

- 4.1 ACS is an umbrella term for the suspicion or confirmation of myocardial infarction or unstable angina events which occur when the blood supply to the heart is suddenly blocked, otherwise known as myocardial ischaemia (AHA 2022). Patients with acute coronary syndrome are further divided into ST elevation myocardial infarction (STEMI) or non-ST elevation acute coronary syndrome (NSTEMI).
- 4.2 STEMI is a life-threatening event usually caused by acute thrombotic occlusion of a coronary artery. Management involves immediate treatment with dual antiplatelet therapy and emergency reperfusion therapy with either PCI or thrombolytic therapy (if primary PCI is not available; Australian Therapeutic Guidelines 2023). Patients with acute myocardial ischaemia without persistent ST elevation on an electrocardiogram (ECG) are diagnosed as having NSTEMI, which is further divided into 2 groups based on cardiac troponin levels: non-ST elevation myocardial infarction (NSTEMI), defined by elevated troponin; and unstable angina, defined as myocardial ischaemia at rest or on minimal exertion but with normal troponin levels. Management of confirmed NSTEMI involves stratification by risk to determine whether invasive management is required (i.e. coronary angiography and revascularisation within 2 hours of diagnosis for very high risk and within 24 hours for high risk; Australian Therapeutic Guidelines 2023).
- 4.3 Prasugrel is an oral adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class. It inhibits platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. Since platelets are involved in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of death and the rate of ischaemic cardiovascular events such as myocardial infarction (MI) or stroke.

- 4.4 The recommended dosing of prasugrel for the treatment of ACS indicated for PCI is a 60 mg loading dose (6 x 10 mg oral tablets; immediately following diagnosis for patients undergoing primary PCI for STEMI, or after the coronary anatomy is known among those undergoing urgent PCI for NSTEMACS), followed by a maintenance dose of 10 mg oral tablet, once daily, with concomitant aspirin. For patients aged ≥ 75 years or weighing < 60 kg, a 5 mg once daily maintenance dose is recommended.
- 4.5 The proposed clinical management algorithm positioned prasugrel as an alternative to ticagrelor or clopidogrel in the treatment of STEMI or high to very high risk NSTEMACS in the acute and long-term setting, noting that ticagrelor or prasugrel are the preferred P2Y₁₂ inhibitors, unless contraindicated. Prasugrel is not recommended for patients who have a prior history of stroke or transient ischaemic attack (due to increased risk of bleeding).
- 4.6 The ESC considered that the use of prasugrel, if recommended, was likely to be small as the treatment of ACS is protocol driven and the use of dual antiplatelet therapy (DAPT) prior to angiography in STEMI and NSTEMACS is standard. Also, unlike clopidogrel or ticagrelor which have a broad ACS indication, prasugrel cannot be given to patients who have had a stroke or transient ischemic attack. The ESC noted that for patients with STEMI, although prasugrel can be commenced pre-angiogram it should be stopped if a PCI is not performed; whereas patients can continue clopidogrel and ticagrelor if a PCI is not performed. For patients with NSTEMACS, unlike clopidogrel and ticagrelor, prasugrel cannot be commenced until coronary anatomy is known and a PCI is planned or performed; this means that either DAPT must be withheld until the angioplasty has been performed or patients start on clopidogrel or ticagrelor and then change to prasugrel post PCI. If antiplatelet therapy is changed during ACS, then patients need to receive another loading dose of the new agent. Further the ESC noted that prasugrel, unlike clopidogrel or ticagrelor, requires dose adjustment for patients ≥ 75 years of age or < 60 kg.

For more detail on PBAC's view, see Section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated ticagrelor, in combination with aspirin, as the main comparator. Ticagrelor, like prasugrel, is a P2Y₁₂ inhibitor, but has a different mechanism of action and activation time. Ticagrelor inhibits platelet activation and aggregation by reversibly interacting with the platelet P2Y₁₂ ADP receptor and has peak effect approximately 2 hours after dosing (compared to approximately 1 hour after dosing for prasugrel).
- 5.2 The submission nominated clopidogrel, in combination with aspirin, as a relevant secondary comparator. Clopidogrel is a P2Y₁₂ inhibitor in the same therapeutic class as both prasugrel and ticagrelor. Clopidogrel irreversibly blocks ADP binding and P2Y₁₂ receptor activation. In the original July 2009 PBAC consideration of prasugrel, the PBAC considered that clopidogrel was the relevant comparator. Ticagrelor was not a PBS-listed therapy for ACS at that time.

5.3 The main arguments provided in support of ticagrelor over clopidogrel as the main comparator were:

- According to the Australian Therapeutic Guidelines (2023), the preferred P2Y12 inhibitors for patients undergoing PCI for ACS are prasugrel and ticagrelor (rather than clopidogrel), due to a more rapid onset of action, less variable platelet inhibition and better clinical outcomes than clopidogrel. Clopidogrel is recommended for patients contraindicated to prasugrel and ticagrelor.
- PBS service data over the previous 10 years show a steady increase in ticagrelor scripts and a gradual decrease in clopidogrel scripts over time.
- Ticagrelor was PBS listed on the basis of a clinical claim of superiority to clopidogrel (Ticagrelor PSD, July 2011 PBAC meeting).

5.4 Given Australian and overseas guidelines recommend the use of prasugrel and ticagrelor over clopidogrel for patients undergoing PCI for ACS, the ESC considered that ticagrelor was a suitable comparator; however, the ESC considered that clopidogrel could also be a suitable comparator. The ESC noted that PBS service data are not a reliable indicator of choice of therapy in Australia – there has been a sharp decline in recorded clopidogrel prescriptions as the DPMQ for clopidogrel has fallen under the general patient copayment. In addition, the unrestricted listing for clopidogrel means that it is not possible to determine the indication for each prescription.

5.5 The ESC considered that prasugrel will most often substitute for clopidogrel over ticagrelor. Further, the ESC considered, given the more limited role of prasugrel in ACS (see paragraph 4.6) and the uncertainty of the superiority claim (see paragraph 6.28), that ticagrelor would likely remain the preferred treatment option and would rarely be replaced by prasugrel. The ESC also noted that ticagrelor is a reversible P2Y12 inhibitor, whereas prasugrel is an irreversible inhibitor and that this may also reduce substitution of ticagrelor.

For more detail on PBAC's view, see Section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from NACCHO, the national peak body representing 145 Aboriginal Community Controlled Health Organisations (ACCHOs). the organisation (1) via the Consumer Comments facility on the PBS website. NACCHO stated that there are a small number of patients who are accessing prasugrel privately.

Clinical trials

- 6.3 The submission was based on one head-to-head trial (n=4,018) comparing prasugrel and ticagrelor (ISAR-REACT 5), and two head-to-head trials comparing prasugrel and clopidogrel, TRITON-TIMI 38 (n=13,608), and ELDERLY-ACS II (n=1,455). Evidence from the TRITON-TIMI 38 trial was the basis of the July 2009 PBAC consideration of prasugrel.
- 6.4 Overall, the submission's literature searches were not satisfactory. An independent search located several other potentially relevant trials of prasugrel and ticagrelor as well as additional publications relating to the main clinical trial of prasugrel and ticagrelor (ISAR-REACT 5) that were not identified in the submission's searches. Additionally, a NICE evidence review of dual antiplatelet therapy in ACS (2020) and other published meta-analyses listed a number of potentially relevant randomised controlled trials that were not included in the submission's results or were inappropriately excluded from further consideration (see paragraphs 6.17 to 6.20). The Pre-Sub-Committee Response, noting that the body of evidence was very large, acknowledged that the systematic literature review did not identify all the relevant literature, but reiterated that the submission was based on a recent, large, head-to-head trial comparing prasugrel with ticagrelor.
- 6.5 Details of the trials presented in the submission are provided in Table 3. Clinical trial reports were not available for any of the included trials.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Prasugrel versus ticagrelor		
ISAR-REACT 5	Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes.	<i>N Engl J Med.</i> 2019;381(16):1524-1534.
	Coughlan JJ, AYTEKIN A, Ndrepepa G, et al. Twelve-month clinical outcomes in patients with acute coronary syndrome undergoing complex percutaneous coronary intervention: insights from the ISAR-REACT 5 trial.	<i>Eur Heart J Acute Cardiovasc Care.</i> 2021;10(10):1117-1124.
	Valina C, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes.	<i>J Am Coll Cardiol.</i> 2020; 76(21):2436-2446.
	Coughlan JJ, AYTEKIN A, LAHU S, et al. Ticagrelor or prasugrel for patients with acute coronary syndrome treated with percutaneous coronary intervention: A prespecified subgroup analysis of a randomised clinical trial.	<i>JAMA Cardiol.</i> 2021;6(10):1121–1129.
	Gewalt S, LAHU S, Ndrepepa G, et al. Efficacy and Safety of Ticagrelor Versus Prasugrel in Women and Men with Acute Coronary Syndrome: A Pre-specified, Sex-Specific Analysis of the ISAR-REACT 5 Trial.	<i>J Atheroscler Thromb.</i> 2022; 29(5):747-761.
Prasugrel versus clopidogrel		
TRITON-TIMI 38	Wiviott S, Braunwald E, McCabe C, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes.	<i>N Engl J Med.</i> 2007 Nov 15;357:2001-2015.
	Mariani M, Mariani G, De Servi S. Efficacy and safety of prasugrel compared with clopidogrel in patients with acute coronary syndromes: results of TRITON-TIMI 38 trials.	<i>Expert Rev Cardiovasc Ther.</i> 2009 Jan;7(1):17-23.
	Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) analysis.	<i>J Am Coll Cardiol.</i> 2008 May 27;51(21):2028-33.
	Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial.	<i>Eur Heart J.</i> 2008 Oct;29(20):2473-9.
	Wiviott SD, Desai N, Murphy SA, Musumeci G, Ragosta M, Antman EM, Braunwald E. Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies.	<i>Am J Cardiol.</i> 2011 Oct 1;108(7):905-11.
	Michelson AD, Frelinger AL 3rd, Braunwald E, Downey WE, Angiolillo DJ, Xenopoulos NP, Jakubowski JA, Li Y, Murphy SA, Qin J, McCabe CH, Antman EM, Wiviott SD; TRITON-TIMI 38 Investigators. Pharmacodynamic assessment of platelet inhibition by prasugrel vs clopidogrel in the TRITON-TIMI 38 trial.	<i>Eur Heart J.</i> 2009 Jul;30(14):1753-63.
	Franz-Josef Neumann. Balancing efficacy and safety in the TRITON-TIMI 38 trial.	<i>Eur Heart J Supplements.</i> 2009; 11: G14-G17.
	De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical outcomes for prasugrel versus clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction: an analysis from the TRITON-TIMI 38 trial.	<i>Eur Heart J Acute Cardiovasc Care.</i> 2014; 3(4):363-72.

Trial ID	Protocol title/ Publication title	Publication citation
ELDERLY ACS II	Savonitto S, Ferri LA, Piatti L, et al. Comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularisation.	<i>Circulation</i> 2018; 137(23):2435-2445.
	Montalto C, Crimi G, Fortuni F, et al. Use of low-dose prasugrel vs clopidogrel in elderly patients undergoing complex or non-complex PCI for acute coronary syndromes: insights from the Elderly ACS 2 study.	<i>Eur Heart J.</i> 2019; 40(1): ehz747.0074
	Crimi G, Morici N, Ferrario M, et al. Time course of ischemic and bleeding burden in elderly patients with acute coronary syndromes randomised to low-dose prasugrel or clopidogrel.	<i>J Am Heart Assoc.</i> 2019; 8(2): e010956.

Source: Source: Table 2-3, pp46-48 of the submission.

6.6 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Prasugrel 5 mg or 10 mg/day^a versus ticagrelor 90 mg twice daily (both with concomitant aspirin)						
ISAR-REACT 5	4,018	Phase 4, MC, R, OL, PG 12 months	Moderate	Adults hospitalised with ACS with planned invasive strategy	Composite: death from any cause, MI, or stroke at 1 year; definite or possible stent thrombosis, major bleeding at 1 year	Incidence of MI, stroke, major bleeding, all-cause mortality
Prasugrel 10 mg/day versus clopidogrel 75 mg/day (both with concomitant aspirin)						
TRITON-TIMI 38	13,608	Phase 3, MC, R, DB, PG 15 months	Low	Patients with moderate-to high-risk ACS undergoing PCI	Composite: CV death, non-fatal MI, non-fatal stroke at 15 months; urgent target-vessel revascularisation, stent thrombosis, TIMI major bleeding not related to CABG.	-
Prasugrel 5 mg/day versus clopidogrel 75 mg/day (both with concomitant aspirin)						
ELDERLY-ACS II	1,455	MC, R, OL, PG	Moderate	Patients aged >74 years hospitalised with ACS and candidates for early PCI	Composite: all-cause mortality, MI, disabling stroke, rehospitalization for CV causes or bleeding within 1 year; CV mortality, any stroke, bleeding within 12 months	-

Source: Section 2.3, pp51-60 of the submission.

Abbreviations: DB, double blind; MC, multi-centre; OL, open label; PG, parallel group; R, randomised.

^a In the ISAR-REACT 5 trial, a lower 5 mg prasugrel maintenance dose was used for patients aged 75 or older, or weighing under 60 kg. However, patient characteristics or results for this subgroup were not presented separately in the trial publications.

6.7 The risk of bias in the ISAR-REACT 5 and ELDERLY-ACS II trials was moderate as although the trials were open-label, they used objective measures in endpoint analyses and event adjudication by blinded event adjudication committee members.

Comparative effectiveness

6.8 Results for the primary composite outcome and key secondary efficacy outcomes from the ISAR-REACT 5 trial are summarised in Table 5.

Table 5: Primary and key secondary efficacy endpoints at 12 months in the ISAR-REACT 5 trial (ITT population)

Endpoint	Ticagrelor (N=2,012)	Prasugrel (N=2,006)	Hazard Ratio (95% CI)
Death from any cause, MI, or stroke (primary endpoint)	184 (9.3)	137 (6.9)	1.36 (1.09, 1.70)
Death, n (%)			
From any cause	90 (4.5)	73 (3.7)	1.23 (0.91, 1.68)
From CV cause	63 (3.2)	59 (3.0)	NR
From non-CV cause	27 (1.4)	14 (0.7)	NR
MI, n (%)	96 (4.8)	60 (3.0)	1.63 (1.18, 2.25)
Stroke, any, n (%)	22 (1.1)	19 (1.0)	1.17 (0.63, 2.15)
Definite or probable stent thrombosis, n (%)	26 (1.3)	20 (1.0)	1.30 (0.72, 2.33)

Source: Table 2-17, p81 of the submission.

Abbreviations: CV, cardiovascular; MI, myocardial infarction

Note: Results are presented for ticagrelor versus prasugrel; a hazard ratio greater than 1 indicates a lower risk in the prasugrel arm.

- 6.9 The primary composite endpoint of death from any cause, MI or stroke at 1 year after randomisation occurred in a larger proportion of patients in the ticagrelor group than in the prasugrel group (HR = 1.36, 95% CI: 1.09, 1.70). The difference between treatments for the composite outcome appeared to be driven by the difference in occurrence of myocardial infarction (ticagrelor 4.8%, prasugrel 3.0%, HR = 1.63; 95% CI: 1.18, 2.25).
- 6.10 The finding of a lower incidence of the primary end point in the prasugrel group than in the ticagrelor group was not anticipated during the sample-size calculation for the trial. The study authors (Schupke 2019) noted that the incidence of the primary endpoint in the ticagrelor group (9.3%) was close to the 10% event rate predicted for that group during the trial's design, but in the prasugrel group, the incidence (6.9%) was much lower than predicted (12.9%). The incidence of MI was much lower in the trial than in the previous pivotal prasugrel trial, TRITON TIMI 38, with the study authors suggesting this may be partly due to differing definitions of MI.
- 6.11 The ESC considered that the results for the analysis of comparative efficacy should be interpreted with caution. There were 20.4% of patients in each arm of the trial discharged from hospital without their allocated treatment, including 8.5% of patients in the ticagrelor arm and 9.2% in the prasugrel arm who did not have confirmation of an ACS diagnosis. An additional 12.1% of patients in the ticagrelor arm and 9.9% of patients in the prasugrel arm discontinued their assigned treatments post-discharge.
- 6.12 In a supplement to the trial publication (Schupke 2019), an 'on treatment' analysis was described in which the occurrence of the primary endpoint was assessed in a subset of patients discharged on their study medication (1,602 ticagrelor-treated patients and 1,596 prasugrel patients), in the time period from hospital discharge until discontinuation of treatment or end of follow-up. The authors reported that there was no significant difference between treatments in the occurrence of the primary outcome (92/1,602 (5.7%) in the ticagrelor arm and 71/1,596 (4.5%) in the prasugrel arm; HR = 1.34, 95% CI: 0.98, 1.82). No further details were provided regarding this analysis.

6.13 Results of the primary and key secondary efficacy endpoints from the TRITON-TIMI 38 trial, comparing prasugrel and clopidogrel, are summarised in Table 6.

Table 6: Primary and key secondary endpoints at 15 months in the TRITON-TIMI 38 trial (ITT population)

Endpoint	Prasugrel (N=6,813)	Clopidogrel (N=6,795)	Hazard Ratio (95% CI)
Death from CV causes, non-fatal MI, or non-fatal stroke (primary endpoint)	643 (9.9)	781 (12.1)	0.81 (0.73, 0.90)
Death from CV causes, non-fatal MI, or urgent target-vessel revascularisation, n (%)	652 (10.0)	798 (12.3)	0.81 (0.73, 0.89)
Death from any cause, non-fatal MI, or non-fatal stroke, n (%)	692 (10.7)	822 (12.7)	0.83 (0.75, 0.92)
Urgent target-vessel revascularisation, n (%)	156 (2.5)	233 (3.7)	0.66 (0.54, 0.81)
Death from CV causes, non-fatal MI, non-fatal stroke, or rehospitalisation for ischaemia, n (%)	797 (12.3)	938 (14.6)	0.84 (0.76, 0.92)
Stent thrombosis, n (%)	68 (1.1)	142 (2.4)	0.48 (0.36, 0.64)

Source: Table 2-17, p81 of the submission.

Abbreviations: CV, cardiovascular; MI, myocardial infarction

6.14 The composite primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke during the follow-up period) occurred in a smaller proportion of patients in the prasugrel group than the clopidogrel group (HR = 0.81, 95% CI: 0.73, 0.90). The results of the primary outcome were driven by a statistically significant difference in the risk of patients experiencing non-fatal MI (in favour of prasugrel) over the 15 months (HR = 0.76, 95% CI: 0.67, 0.85). There were no statistically significant differences between treatments in the other components of the composite outcome (death from cardiovascular causes, non-fatal stroke, death from any cause).

6.15 Results for the primary composite outcome and key secondary outcomes in the ELDERLY ACS II trial, comparing low dose prasugrel and standard clopidogrel in patients aged 75 and older, are summarised in Table 7.

Table 7: Primary and key secondary endpoints at 12 months in the ELDERLY-ACS II trial (ITT population)

Endpoint	Prasugrel (N=713)	Clopidogrel (N=730)	Hazard Ratio (95% CI)
All cause mortality, MI, disabling stroke, and rehospitalisation for CV causes or severe bleeding (primary endpoint), n (%)	121 (17.0)	121 (16.6)	1.007 (0.78, 1.30)
All cause death and MI, n (%)	60 (8.4)	60 (8.2)	1.02 (0.71, 1.45)
Cardiovascular death, n (%)	26 (3.6)	31 (4.2)	0.85 (0.51, 1.4)
Strokes, n (%)	7 (1.0)	13 (1.8)	0.55 (0.22, 1.37)
Definite/probable stent thrombosis, n (%)	5 (0.7)	14 (1.9)	0.36 (0.13, 1.00) ^a

Source: Table 2-22, p88 of the submission.

Abbreviations: CV, cardiovascular; MI, myocardial infarction

^a Odds ratio

6.16 In the ELDERLY-ACS II trial, similar rates of the primary composite outcome (all-cause mortality, MI, disabling stroke, hospitalisation for CV causes or bleeding within 1 year) were observed in the group assigned to prasugrel 5 mg maintenance dose (17.0%) compared with standard dose clopidogrel 75 mg (16.6%; HR = 1.01, 95% CI: 0.78, 1.30). Results for the secondary outcomes were consistent with the primary endpoint, with no statistically significant differences observed between treatment arms for any efficacy outcome. The study authors noted that the results should be interpreted in light of the premature termination of the trial due to futility, with a lower than

expected event rate and lower than planned number of patients enrolled meaning that the study analysis was underpowered.

- 6.17 The results of the NICE Evidence Review (NICE Evidence Review NG185, 2020), which included a systematic review, pairwise meta-analysis and network meta-analysis of randomised trials comparing any of clopidogrel, prasugrel, or ticagrelor (in combination with aspirin) in an ACS population, were summarised during the evaluation.
- 6.18 In brief, results of the pairwise meta-analyses (at 30 days and 1 year) were generally consistent with the evidence presented in the submission, with prasugrel being associated with a lower risk of MI compared to ticagrelor and clopidogrel, with a higher risk of major bleeding compared to clopidogrel, but no difference compared to ticagrelor.
- 6.19 Results of the network meta-analyses, based on outcomes measured at 30 days, indicated that prasugrel may be more effective than clopidogrel and ticagrelor in terms of all-cause mortality and stroke; prasugrel may be more effective than clopidogrel, but less effective than ticagrelor in terms of MI; and there were no differences between treatments in terms of major bleeding. The ESC considered that outcomes at 30 days had low relevance to the population requested in the submission and that longer term data was more important.
- 6.20 The NICE Evidence Review stated that a network meta-analysis of 1-year outcomes was considered, but there was inconsistency in the network between the direct and indirect estimates of treatment effect, and it was therefore considered inappropriate to undertake a network meta-analysis. The ESC considered that there was considerable uncertainty in the results at ≥ 1 year and that it was most likely that there were only small differences between the treatments.

Comparative harms

- 6.21 The incidence of major bleeding (Bleeding Academic Research Consortium classification (BARC) type 3, 4, or 5, with a higher number indicating more serious bleeding) at 1 year after randomisation was a key secondary safety outcome in the ISAR-REACT 5 trial, measured in the modified intention to treat (ITT) population of patients who received at least one dose of their allocated treatment. There were differences between treatment arms in the patients excluded from the safety analysis, with 233 (11.6%) patients excluded from the prasugrel arm of the trial, compared to 23 (1.1%) patients from the ticagrelor arm. Bleeding incidence was higher in the ticagrelor group (95/1,989; 5.4%) than in the prasugrel group (80/1,733; 4.8%); however, the results were not statistically significantly different (HR = 1.12; 95% CI: 0.83, 1.51). The majority of events in each treatment arm were rated BARC 3a (overt bleeding with a decrease in haemoglobin level of 3 to < 5 g/dL or any transfusion) or 3b (overt bleeding with decrease in haemoglobin level of ≥ 5 g/dL or leading to cardiac tamponade, surgical intervention or the use of intravenous vasoactive agents). Four patients in each arm experienced BARC 5a/5b bleeding (probably or definite fatal bleeding).

- 6.22 No other adverse event data were reported for the ISAR-REACT 5 trial.
- 6.23 In the TRITON-TIMI 38 trial, patients in the prasugrel group experienced a higher incidence of the key safety endpoint, thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary-artery bypass grafting (2.4%) compared to clopidogrel (1.8%) over 15 months (HR = 1.32; 95% CI: 1.03, 1.68).
- 6.24 In the ELDERLY-ACS II trial, the occurrence of BARC 2 bleeding was higher in the prasugrel arm (2.2%) compared to the clopidogrel arm (1.1%), but the difference was not statistically significantly different (HR = 1.52, 95% CI: 0.85, 3.16). Similarly, BARC 2 or greater bleeding was higher in the prasugrel arm (4.1% vs 2.7%; HR = 1.53, 95% CI: 0.85, 3.16), but not statistically significantly different to the clopidogrel arm. Other safety outcomes were not reported in the available ELDERLY-ACS II trial publications.

Benefits/harms

- 6.25 On the basis of the direct evidence presented in the submission, for every 100 patients treated with prasugrel in comparison with ticagrelor (both in combination with aspirin) over a maximum of 12 months:
- Approximately 2 fewer patients will experience a major ischaemic event, consisting of either death from any cause, a non-fatal MI or a non-fatal stroke, with this being almost entirely due to reduced non-fatal MI.
 - There would be no difference in the number of people who die from any cause, or who have a stroke, or who have a stent thrombosis (a blood clot in a stent implant).
 - There would be no difference in the number of people experiencing a major bleeding event.
- 6.26 On the basis of the direct evidence presented in the submission, for every 100 patients treated with prasugrel in comparison with clopidogrel (both in combination with aspirin) over a maximum of 15 months:
- Approximately 2 fewer patients will experience a major ischaemic event, consisting of either death from cardiovascular causes, a non-fatal MI or a non-fatal stroke.
 - Approximately 1 less patient will require urgent target-vessel revascularisation.
 - Approximately 1 additional patient will have a bleeding event requiring transfusion.

Clinical claim

- 6.27 The submission described prasugrel (in combination with aspirin), as superior in terms of effectiveness and non-inferior in terms of safety compared with ticagrelor (in combination with aspirin).
- 6.28 This ESC considered that the claim that prasugrel was superior to ticagrelor in terms of efficacy was not adequately supported given:

- The robustness of the key evidence supporting the prasugrel versus ticagrelor comparison (ISAR-REACT 5) was uncertain as it was an open-label trial with differential discontinuation between treatment arms.
 - The submission's literature search to identify relevant clinical trials was unsatisfactory and the evidence presented in the submission did not capture the full body of evidence comparing prasugrel with ticagrelor.
 - The NICE evaluation concluded that there were conflicting results in trials that reported results at one year between clopidogrel, ticagrelor and prasugrel that prevented an appropriate meta-analysis from being performed.
- 6.29 Hence, the ESC considered that, as the superiority of prasugrel over ticagrelor was not demonstrated definitively, a claim of non-inferiority was more appropriate.
- 6.30 The PBAC agreed that the claim of superior comparative effectiveness was not adequately supported by the data and considered that prasugrel was likely non-inferior to ticagrelor.
- 6.31 The ESC considered that the claim that prasugrel was non-inferior compared to ticagrelor in terms of safety was likely supported by the data presented.
- 6.32 The PBAC agreed that the claim of non-inferior comparative safety was reasonable.
- 6.33 The submission did not provide a clinical claim for the comparison of prasugrel to clopidogrel, arguing that the PBAC previously accepted that the superior comparative clinical benefit of prasugrel over clopidogrel, in terms of reduced non-fatal MI events, marginally outweighed the inferior comparative safety profile in terms of a higher incidence of adverse bleeding events (Section 12, Prasugrel PSD, July 2009 PBAC meeting). The ESC considered that this remained reasonable but noted that there was considerable uncertainty in the magnitude of this difference and that it was likely very small. The submission provided additional evidence from the ELDERLY-ACS II trial which found no difference in efficacy and safety between prasugrel low dose (5 mg) and clopidogrel standard dose in elderly patients aged 75 years or older.

Economic analysis

- 6.34 The submission presented a modelled economic evaluation of prasugrel versus ticagrelor (both in combination with aspirin) in patients with ACS who are indicated for PCI. An economic evaluation comparing prasugrel with clopidogrel was not presented.
- 6.35 The economic analysis was based on the results of the ISAR-REACT 5 trial, with additional modelled data. The type of economic evaluation presented was a cost-effectiveness/cost-utility analysis. A cost-effectiveness analysis is appropriate if the claim of superior efficacy is accepted. However, given the submission proposed a lower price for prasugrel compared to ticagrelor, with improved/similar treatment efficacy, a cost-utility analysis will always be dominant. Given uncertainty with the robustness of the superiority claim, the ESC considered that if the PBAC accepts ticagrelor as a comparator, then a cost-minimisation approach versus ticagrelor may

be a more appropriate approach. If the PBAC considers that clopidogrel is also a relevant comparator, then the ESC considered that an economic analysis versus a weighted combination of clopidogrel and ticagrelor would be appropriate. The ESC noted that given the substantially reduced price of clopidogrel since the 2009 analysis, the cost-effective price of prasugrel was also likely to be lower than accepted in 2009.

- 6.36 The economic model was based on use of the prasugrel 10 mg tablet only. The cost-effectiveness of prasugrel 5 mg in an older cohort (≥ 75 years), or patients weighing less than 60 kg, was not assessed.
- 6.37 Table 8 summarises the key components of the economic evaluation.

Table 8: Key components of the economic evaluation

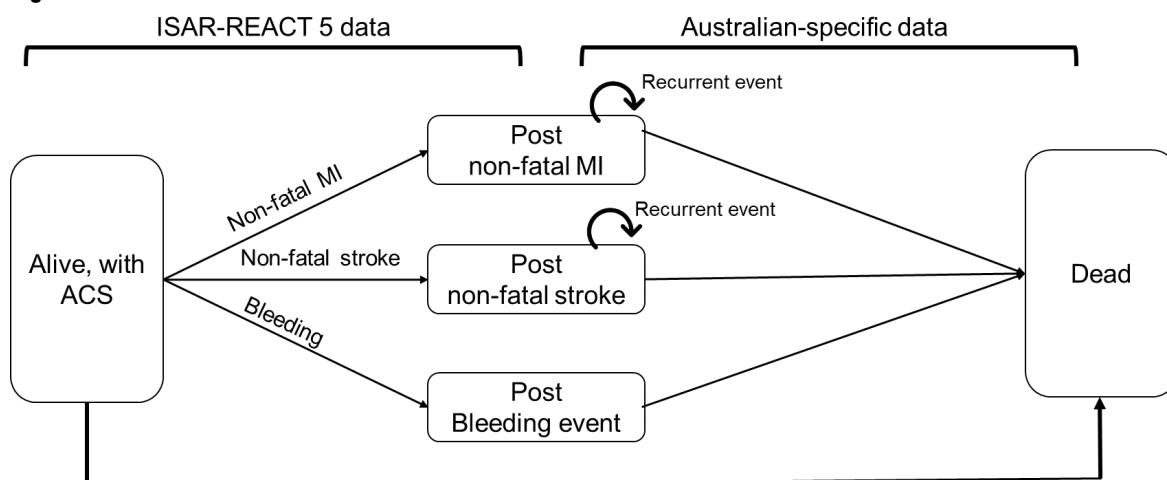
Component	Description
Type of analysis	Cost effectiveness analysis and cost utility analysis
Treatments	Prasugrel and ticagrelor (both in combination with aspirin and other standard care therapies)
Outcomes	Life years; quality adjusted life years
Time horizon	21 years in the model base case versus 1 year in the ISAR-REACT 5 trial
Methods used to generate results	Markov state transition model
Health states	Alive with ACS (no further events); post-MI; post-stroke; post-bleeding; dead. Patients in the post-MI state are at risk of recurrent MI events and patients in the post-stroke state are at risk of recurrent stroke events.
Cycle length	3 months during the first year and 6 months in subsequent years.
Patient characteristics and circumstances of use	The modelled population has a baseline age of 64.5 years and is 23.8% female, based on baseline characteristics in the ISAR-REACT 5 trial. These characteristics were used to inform mortality. It was assumed that patients would receive prasugrel or ticagrelor treatment for 1 year, with perfect adherence and persistence over the year. Patients were assumed to be fully compliant with their standard care therapies over the 21-year duration of the model.
Transition probabilities	Transition probabilities from the alive with ACS health state in the first year were based on the incidence at 12 months of MI, stroke, bleeding and death events in the ISAR-REACT 5 trial. Transitions to the post-MI and post-stroke health states in subsequent years, and probabilities of recurrent MI and stroke events were based on average annual rates of MI and stroke events in the Australian general population, by age and sex from AIHW 2020 (Heart, stroke and vascular disease: Australian facts) weighted by the sex distribution in the ISAR-REACT 5 trial. It was assumed that transitions to the post-bleeding state were the same as for stroke. It was assumed that patients in the post-MI health state could not have stroke or bleeding events; patients in the post-stroke health state could not have MI or bleeding events; and patients in the post-bleeding state could not have any non-fatal events (MI, stroke, bleeding). The ESC considered that these assumptions did not align with clinical outcomes. Transitions to the dead health state from the alive with ACS state in subsequent years were based on average annual rates of cardiovascular death in the Australian general population, by age and sex from AIHW 2021 (GRIM books) weighted by the sex distribution in ISAR-REACT 5. Transitions to the dead health state from the post-MI, post-stroke, and post-bleeding states were based on average annual rates of death (any cause) in the Australian general population, by age and sex from AIHW 2021 (GRIM books), weighted by sex distribution in ISAR-REACT 5.
Health related quality of life	Utilities for the alive with ACS (0.842) and post-MI (0.821) health states were based on utilities reported in the NICE ticagrelor submission, based on utilities derived from the ticagrelor PLATO trial (health economics substudy). The utility for the post-stroke health state (0.720) was claimed to be from a UK longitudinal study of the quality of life of patients with ACS (Pockett 2018), but the utility used in the model could not be verified during the evaluation. The ESC considered that the post-stroke utility should also be based on the value applied in the NICE ticagrelor submission (0.730). It was assumed that patients in the post-bleeding state would have the same utility as the alive with ACS state, due to a lack of data on the long-term quality of life implications of bleeding events. Disutilities associated with recurrent MI and stroke events were not included in the economic model. The disutility associated with bleeding events was based on the assumption that a bleeding event is associated with a loss of 1 quality adjusted life week, reported in a US cost-effectiveness analysis of ticagrelor for ACS (Crespin 2011).

Component	Description
Costs	<p>Prasugrel and ticagrelor costs were based on the proposed and current DPMQs, respectively. The ESC noted that the loading doses of prasugrel and ticagrelor were not accounted for.</p> <p>Standard drug treatments were informed by Australian Therapeutic Guidelines (2023). All patients were assumed to receive a statin, beta blocker, ACE-inhibitor and aspirin. A proportion of patients was assumed to receive ezetimibe (3.6%) and a PCSK9 inhibitor (1.0%). Costs were based on the weighted average DPMQ by utilisation associated with all drugs listed on the PBS within a class.</p> <p>Acute event costs were based on the hospitalisation costs associated with each event, based on relevant AR-DRG costs weighted by the number of separations (NHCCD Cost weights for AR-DRG v10.0, 2020-21; Public Sector). It was assumed that 50% of patients would be hospitalised prior to death.</p> <p>Disease management costs for the post-MI health state were based on Australian data from the CosMIC study (Ioannides-Demos 2010). The same costs were applied to the alive with ACS health state. Disease management costs for the post-stroke health state were based on Australian data from the NEMESIS study (Gloede 2014). The ESC noted that the post-stroke health state costs in the year following a stroke were based on the costs accrued in years 3-5 post stroke. The ESC considered that these might be underestimated and not representative of the true costs. It was assumed that there would be no disease management costs associated with the post-bleeding health state. The ESC considered that this was not reasonable.</p>

Source: Table 3-1, p114 of the submission; Sections 3.3 to 3.6 of the submission; Prasugrel CUA spreadsheet provided with the submission. Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Group; DPMQ, dispensed price for maximum quantity; GRIM, General Record of Incidence of Mortality; MI, myocardial infarction; NHCCD, National Hospital Cost Data Collection; NICE, National Institute for Health and Care Effectiveness; PBS, Pharmaceutical Benefits Scheme; PCSK9, proprotein convertase subtilisin-kexin type 9; UK, United Kingdom; US, United States

6.38 Figure 1 provides an overview of the model structure.

Figure 1: Model structure



Source: Figure 18, p128 of the submission
 Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction

6.39 The Markov model has two main phases: the primary treatment phase (first year of the model), where prasugrel or ticagrelor costs and effects (based on the ISAR-REACT 5 trial) are applied to all patients in each cohort; and a follow-up phase (years 2 to 21 of the model), where outcomes are based on the same risks between treatment arms (based on Australian data) and no costs associated with prasugrel or ticagrelor were applied.

- 6.40 All patients begin the model in the 'alive, with ACS' health state, from which they can experience a non-fatal MI, non-fatal stroke, non-fatal bleeding event or die (in the first year of the model, patients in the alive with ACS state can die due to all-cause mortality based on the ISAR-REACT 5 trial; in subsequent years, patients are at risk of cardiovascular mortality only, based on data from the Australian general population).
- 6.41 After a non-fatal event (MI, stroke, bleeding event), patients move to their respective health states (post-MI, post-stroke, post-bleeding). In the post-MI and post-stroke health states, patients can experience a recurrent event of the same type or die due to all-cause mortality. In the post-bleeding health state, patients are unable to experience MI, stroke, or further bleeding events and can only die due to all-cause mortality. The ESC considered that the assumption that patients who experience a bleeding event are protected from ever experiencing an MI or stroke was not appropriate and did not reflect the clinical pathway of the disease. The risks of recurrent MI and stroke events and all-cause mortality in the post-MI, post-stroke and post-bleeding health states were based on data from the Australian general population. The submission acknowledged that it is highly likely that patients with ACS would have a higher risk of subsequent non-fatal and fatal events, but argued there was a lack of long-term data regarding the specific increases in risk. The ESC considered that this assumption was not adequately justified and that the risk of having a subsequent event, particularly in the year following the first event, should be adjusted to better reflect clinical outcomes. Overall, the ESC considered that the model structure, which did not allow the movement of patients between health states, was unreliable for decision making and inconsistent with other published models.
- 6.42 A number of errors and issues with the modelled economic evaluation were identified that could be corrected during the evaluation:
- The submission stated that a 5% discount rate was applied to costs and outcomes, however, the base case results of the economic model were derived using a 3% discount rate.
 - Prasugrel, ticagrelor and standard care drug costs were overestimated by a factor of 4 (the 4-weekly costs were multiplied by the number of weeks in a cycle).
 - Life years and quality adjusted life years (QALYs) were not adjusted for the cycle length (3 months in the first year, 6 months in subsequent years), resulting in an overestimation of incremental benefit by a factor of more than 2.
 - The all-cause mortality rate for patients in the alive with ACS health state beyond the trial was inappropriately based on the cardiovascular mortality rate in the Australian general population, which is substantially lower than the all-cause mortality rate in the Australian general population (applied to other health states).
 - Other calculation errors (misapplication of the hazard ratio to risks of recurrent events in the first year of the model; misapplication of the disutility of bleeding

events; additional errors in the calculation of standard care drug costs; errors in the calculation of disease management costs).

- 6.43 The ESC noted that a number of other issues with the model were identified that could not be addressed during the evaluation:
- The risks of MI, stroke and death beyond the trial were based on risks in the Australian general population, which are expected to be lower than those for patients with ACS indicated for PCI (including those who experienced subsequent MI and stroke events).
 - All patients were assumed to receive 1 year of prasugrel or ticagrelor treatment, which was inconsistent with the submission's claim that a large component of the target population could be considered at high risk of recurrent ischaemic events, and therefore likely to receive ongoing treatment with antiplatelet therapy.
 - Patients in the post-bleeding state are protected from ever experiencing an MI or stroke, and do not incur disease management costs; while patients in the alive with ACS, post-MI, and post-stroke health states accrue disease management costs.
- 6.44 The submission claimed that disutilities associated with MI and stroke events were not applied, as lower utilities associated with the post-MI and post-stroke health states were applied each cycle until the patient dies, which was considered conservative. The ESC noted that this approach may not be conservative if patients experience further recovery following an event, particularly in the case of MI events. Further, the ESC considered that patients who experience recurrent events would have lower utility scores which should be reflected in the model in the form of a disutility.
- 6.45 Table 9 summarises the incremental difference in health outcomes estimated in the economic evaluation, as presented in the submission, and corrected during the evaluation.

Table 9: Disaggregated summary of health outcomes included in the economic evaluation

Health outcome	Estimates in the submission			Corrected during the evaluation		
	Prasugrel + aspirin	Ticagrelor + aspirin	Increment	Prasugrel + aspirin	Ticagrelor + aspirin	Increment
Events						
- non-fatal MI	0.1698	0.1837	-0.0139	0.1021	0.1184	-0.0162
- non-fatal stroke	0.1070	0.1053	0.0017	0.0548	0.0547	0.0001
- non-fatal bleeding	0.1373	0.1364	0.0009	0.0869	0.0876	-0.0007
- death	0.3950	0.4114	-0.0164	0.8808	0.8818	-0.0010
Life years (undiscounted)	37.1629	36.5355	0.6274	10.5422	10.4568	0.0854
- alive with ACS	31.9689	31.0145	0.9544	8.6773	8.4169	0.2603
- post-MI	2.1083	2.4250	-0.3166	0.7579	0.9165	-0.1586
- post-stroke	1.1705	1.1671	0.0034	0.3761	0.3802	-0.0041
- post-bleeding	1.9152	1.9289	-0.0137	0.7309	0.7431	-0.0122
Life years (discounted)	28.0742	27.6342	0.4389	7.5314	7.4714	0.0599
QALYs (discounted)	23.5008	23.1257	0.3752	6.3030	6.2497	0.0534
- alive with ACS	20.5576	19.9557	0.6019	5.3616	5.2038	0.1577
- post-MI	1.2169	1.4293	-0.2124	0.3857	0.4787	-0.0930
- post-stroke	0.5700	0.5713	-0.0013	0.1602	0.1632	-0.0030
- post-bleeding	1.1663	1.1793	-0.0131	0.3970	0.4053	-0.0083
- MI events	0	0	0	0	0	0
- stroke events	0	0	0	0	0	0
- bleeding events	-0.0099	-0.0099	0	-0.0014	-0.0014	-0.0000

Source: Table 3-14, p147 of the submission and Prasugrel CUA spreadsheet provided with the submission

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; QALY, quality adjusted life year

- 6.46 The difference in quality adjusted life years between treatment arms was primarily driven by an increase in survival in patients treated with prasugrel versus ticagrelor. The ESC noted that the application of a mortality benefit was not supported by the clinical data. Due to the lack of an adjustment for cycle length (3 months in the first year; 6 months in subsequent years), the submission's estimates of undiscounted life years in the prasugrel and ticagrelor treatment arms were implausible (37.2 and 36.5 years, respectively); far exceeding the time horizon of the model (21 years). Correcting for the errors in the model that could be corrected during the evaluation (see paragraphs 6.42 and 6.43 above) resulted in substantially smaller life years and QALYs gained for prasugrel versus ticagrelor.
- 6.47 The results of the modelled economic evaluation, as presented in the submission, and corrected during the evaluation, are summarised in Table 10.

Table 10: Results of the modelled economic evaluation

Component	Prasugrel + aspirin	Ticagrelor + aspirin	Increment
Estimates in the submission			
Costs	\$	\$95,899	\$
Life years	28.0742	27.6342	0.4389
Quality adjusted life years	23.5008	23.1257	0.3752
Incremental cost/life year gained			Prasugrel dominant
Incremental cost/quality adjusted life year gained			Prasugrel dominant
Corrected during the evaluation			
Costs	\$	\$30,461	-\$
Life years	7.5314	7.4714	0.0599
Quality adjusted life years	6.3030	6.2497	0.0534
Incremental cost/life year gained			Prasugrel dominant
Incremental cost/quality adjusted life year gained			Prasugrel dominant

Source: Table 3-55, p146 of the submission and Prasugrel CUA spreadsheet provided with the submission

- 6.48 Based on the economic model, as presented in the submission, treatment with prasugrel was associated with the same costs and higher QALYs (i.e. was dominant) compared to ticagrelor for the treatment of patients with ACS who are indicated for PCI. The submission’s estimates of discounted life years and QALYs in the prasugrel and ticagrelor treatment arms were implausible, exceeding the time horizon of the model (21 years). Correcting for the errors that could be corrected during the evaluation resulted in prasugrel remaining dominant, with lower costs for prasugrel compared to ticagrelor, and benefits in terms of life years and QALYs gained; although the magnitude of benefit was substantially smaller than estimated in the submission. However, a number of issues with the model could not be corrected during the evaluation (see paragraph 6.43). Given the issues with the model structure, i.e., that patients cannot move between health states, and the errors that could not be corrected during evaluation, the ESC considered that the economic model was not reliable for decision making.
- 6.49 Given the numerous errors and issues with the modelled economic evaluation; and the lower cost of prasugrel compared with ticagrelor and modelling of improved/similar outcomes, additional sensitivity analyses were not conducted during the evaluation.

Drug cost/patient

- 6.50 Table 11 presents the drug costs for prasugrel in the economic model and financial estimates.

Table 11: Drug cost per patient for prasugrel

	ISAR-REACT 5	Economic model	Financial estimates
Prasugrel dose distribution	NR ^a	5 mg: 0% 10 mg: 100%	5 mg: 38.61% 10 mg: 61.39%
Treatment adherence	NR ^b	100%	100%
Treatment persistence	NR ^c	100%	100%
Treatment duration	1 year	1 year	1 year
Drug cost per patient	-	\$ ^d	\$ ^e

Source: ISAR-REACT 5 trial publication (Schupke 2019); 'Prasugrel CUA' and 'Prasugrel Section 4 workbook' spreadsheets provided with the submission.

Abbreviations: DPMQ, dispensed price for maximum quantity; NR, not reported

^a Based on the ISAR-REACT 5 trial publication (Schupke 2019), 5.1% of patients weighed < 60 kg, and 24.4% of patients were aged ≥ 75 years; meeting the recommended criteria for 5 mg prasugrel.

^b The ISAR-REACT 5 trial publication (Schupke 2019) reported that 18 patients in the prasugrel arm did not adhere to the trial regimen and were discontinued from the trial. The definition of treatment adherence was not reported.

^c Based on the ISAR-REACT 5 trial publication (Schupke 2019), 2,006 patients were randomised to prasugrel; 80.7% of patients (1,596/1,978 patients discharged alive) received prasugrel at discharge from hospital (time to discharge not reported); at 1 year follow-up, 12.5% of patients who received prasugrel at discharge (199/1,596 patients) discontinued prasugrel.

^d Calculated as \$█ (DPMQ of 10 mg dose) × 365.25 days per year / 28 days of treatment per pack.

^e Calculated as (38.61% × \$█ [DPMQ for 5 mg dose] + 61.39% × \$█ [DPMQ for 10 mg dose]) × 365.25 days per year / 28 days of treatment per pack.

- 6.51 The only difference in the estimation of prasugrel drug costs between the economic model and financial estimates was in the dose distribution (100% use of the 10 mg dose in the economic model versus 38.61% use of the 5 mg dose and 61.39% use of the 10 mg dose in the financial estimates).
- 6.52 The same assumptions were used to estimate ticagrelor costs per patient in the economic model and financial estimates (\$█; DPMQ of \$█×365.25/28 days; assuming 100% adherence and persistence over a 1-year treatment duration).
- 6.53 The use of clopidogrel was only included in the financial estimates (cost per patient \$222.80 for clopidogrel [DPMQ \$17.08×365.25/28] and \$211.48 for clopidogrel with aspirin [DPMQ \$17.37×365.25/30]; assuming 100% adherence and persistence over a 1-year treatment duration).
- 6.54 The submission did not consider the use of 60-day dispensing of ticagrelor or clopidogrel.

Estimated PBS usage & financial implications

- 6.55 This submission was not considered by DUSC. The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact associated with the PBS/RPBS listing of prasugrel for patients with ACS who are indicated for PCI.
- 6.56 Key inputs used to derive the financial estimates are presented in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Treated population		
Incidence of ACS	265.5 per 100,000. AIHW 2022 Estimating the incidence of stroke and ACS using the National Integrated Health Services Information Analysis Asset; rate of new ACS events in people aged ≥25 years in 2018.	The submission's estimate includes fatal and non-fatal ACS events (15.2% of ACS events in 2018 were fatal; AIHW 2022). The ESC considered that the inclusion of fatal events would overestimate the eligible population. The submission assumed that the incidence of ACS will be constant over the first 6 years of listing. The ESC noted that this was inconsistent with data in the source document (AIHW 2022) which indicated that ACS event rates have been declining over time.
ACS patients undergoing PCI	44.24%. AIHW 2022 Medication use for secondary prevention after coronary heart disease hospitalisation. Proportion of ACS patients with PCI performed during index ACS hospitalisation; weighted by CHD subtype (STEMI, NSTEMI, MI, UA)	The submission's estimate was based on patients who have undergone PCI only. There were transcription errors in the submission's calculation. Correcting these errors resulted in an estimate of 40.77%.
ACS patients without a history of stroke	97%. AIHW 2022 Medication use for secondary prevention after coronary heart disease hospitalisation. Calculated as the complement of the proportion of ACS patients with stroke identified as a comorbidity during the risk assessment period or at the index hospitalisation (3.4%).	-
Uptake	7.3267%. Based on PBS utilisation statistics. In 2020, 7.33% of scripts dispensed for P2Y12 inhibitors (including an adjustment for clopidogrel and clopidogrel with aspirin scripts for the proportion of use in ACS) were for prasugrel.	Prasugrel was delisted in July 2020. Using utilisation data from 2020 may not be representative of utilisation of prasugrel if re-listed on the PBS. The estimate does not account for under-copayment use of clopidogrel and clopidogrel with aspirin. The assumption of constant uptake rates over time was not justified in the submission and was inconsistent with the gradual uptake pattern typically seen with the introduction of a medication. The ESC considered, given the prescribing trends in the years prior to the de-listing of prasugrel, that uptake will likely be lower than predicted by the sponsor.
Treatment utilisation		
Prasugrel, ticagrelor and clopidogrel scripts per patient	13.045. Number of scripts, assuming one year of treatment per incident patient, and assuming perfect adherence and persistence (365.25 days per year/28 days per script).	The submission's estimates do not account for loading doses of prasugrel and ticagrelor. There may be a proportion of patients who are not initiated on dual anti-platelet therapy in hospital, for whom there would be a cost to the PBS. The assumption that all patients would be fully compliant with therapy is unlikely to be representative of clinical practice.
Clopidogrel with aspirin scripts per patient	12.175. Number of scripts, assuming one year of treatment per incident patients, and assuming perfect adherence and persistence (365.25 days per year/30 days per script).	A proportion of patients is likely to receive treatment beyond 1 year. The 2016 DUSC analysis of predicted versus actual utilisation of ticagrelor indicates that approximately 50% of ticagrelor patients received treatment for 1 year or more; and approximately 20% of patients received treatment for 2 years or more.

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Parameter	Value applied and source	Comment
Prasugrel dose distribution	38.61% 5 mg/61.39% 10 mg. Based on the numbers of patients with ACS events in 2018 aged ≥75 years and <75 years from AIHW 2022 Estimating the incidence of stroke and ACS using the National Integrated Health Services Information Analysis Asset.	This estimate does not account for patients aged <75 years who weigh <60 kg, for whom a 5 mg dose is also recommended.
Distribution among substituted therapies	Ticagrelor; 71.81%; clopidogrel: 13.37%; clopidogrel with aspirin: 7.65%. Based on PBS utilisation statistics for P2Y12 inhibitors, with clopidogrel and clopidogrel with aspirin scripts adjusted for the proportion of use in ACS; averaged over 2017-2022. It was assumed that 8.36% of clopidogrel scripts and 3.05% of clopidogrel with aspirin scripts are used for ACS (clopidogrel and clopidogrel with aspirin have an unrestricted listing). This was based on data in Table 2 of the February 2016 DUSC analysis of predicted versus actual utilisation of ticagrelor; which used Streamlined authority codes to identify patients with ACS. At the time, clopidogrel and clopidogrel with aspirin had Streamlined authority codes for prevention of recurrence of MI or unstable angina; prevention of recurrence of ischaemic stroke or transient cerebral ischaemic events; ACS; and cardiac stent insertion (clopidogrel only). In May 2022, the restrictions for clopidogrel and clopidogrel with aspirin were changed from Authority Required (Streamlined) to unrestricted benefit.	Estimates have not been adjusted to remove use of prasugrel from current market estimates and do not sum to 100% (substitution rate 92.84%). The proportions applied to clopidogrel/clopidogrel with aspirin scripts to account for use in ACS could not be verified during the evaluation (based on utilisation of clopidogrel and clopidogrel with aspirin from December 2011 to July 2015). The Streamlined Authority codes used in the DUSC analysis are not mutually exclusive, and there is likely to be overlap between use for ACS and prevention of recurrence of MI or unstable angina. It is unclear whether utilisation patterns from 2011 to 2015 would reflect current utilisation patterns. DUSC estimates of the proportion of clopidogrel/ clopidogrel with aspirin use in ACS were based on estimates that included under-copayment scripts; the submission's estimates of script numbers did not account for under-copayment scripts. The ESC considered that the substitution of prasugrel for ticagrelor and clopidogrel would not be proportional to the PBS utilisation statistics. The ESC considered that prasugrel would most likely substitute for clopidogrel and that ticagrelor will be preferred over prasugrel.
PBS/RPBS costs		
Prasugrel DPMQ	5 mg: \$█; 10 mg: \$█. Proposed DPMQs for prasugrel	The proposed DPMQs are higher than the DPMQs for prasugrel at the time of delisting (5 mg: \$81.44; 10 mg: \$89.22; June 2020 PBS Schedule)
Ticagrelor and clopidogrel DPMQs	Ticagrelor: \$130.81; clopidogrel: \$17.08; clopidogrel with aspirin: \$17.37. Published DPMQs.	The submission did not consider the use of 60-day dispensing for ticagrelor and clopidogrel.
Patient copayment	PBS: \$6.18; RPBS: \$3.67. Based on PBS utilisation statistics for ticagrelor and clopidogrel for the 2022 calendar year.	Weighted average copayments were inappropriately based on 2021 patient copayments (\$41.30 and \$6.60); current patient copayments are \$30.00 for general patients and \$7.30 for concessional patients. It may be more appropriate to use utilisation data for ticagrelor to derive patient copayments for prasugrel and ticagrelor; and utilisation data for clopidogrel and clopidogrel with aspirin to derive patient copayments for clopidogrel and clopidogrel with aspirin, given their DPMQs are below the general patient copayment.

Source: Section 4 of the submission; 'Prasugrel Section 4 workbook' spreadsheet provided with the submission

Abbreviations: ACS, acute coronary syndrome; AIHW, Australian Institute of Health and Welfare; CHD, coronary heart disease; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; UA, unstable angina

6.57 Table 13 summarises the estimated patients treated, scripts dispensed and net cost to the PBS/RPBS of listing prasugrel for the treatment of patients with ACS who are indicated for PCI.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed ^a	2	2	2	2	2	2
Estimated financial implications of prasugrel						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Estimated financial implications for ticagrelor, clopidogrel, and clopidogrel plus aspirin						
Cost to PBS/RPBS less copayments	4	4	4	4	4	4
Net financial implications to the PBS/RPBS						
Net cost to PBS/RPBS	3	3	3	3	3	3

Source: Table 6, p154; Table 7, p155; Tables 9-10, p156 of the submission; and 'Prasugrel Section 4 workbook' spreadsheet provided with the submission

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

^a Assuming each incident patient receives 13.045 scripts (one year of treatment per patient, assuming perfect adherence and persistence). Note: The cost of prasugrel and net cost to the PBS/RPBS were derived from the submission's utilisation and cost model spreadsheet, which did not match estimates presented in Sections 4.2 and 4.4 of the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 20,000 to < 30,000

³ \$0 to < \$10 million

⁴ net cost saving

6.58 The estimated net cost to the PBS/RPBS for prasugrel, including cost offsets associated with substituted use of ticagrelor, clopidogrel, and clopidogrel with aspirin was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a cumulative total of \$0 to < \$10 million over 6 years.

6.59 The ESC considered that the submission's utilisation estimates were likely overestimated as, given the prescribing trends in the years prior to the de-listing of prasugrel, uptake will be lower than predicted. In addition, the ESC noted:

- The distribution of substitution from ticagrelor (71.81%), clopidogrel (7.65%, and clopidogrel with aspirin (13.37%) was uncertain given the adjustment to clopidogrel and clopidogrel with aspirin scripts to account for use in ACS could not be verified and may not reflect current utilisation patterns. The ESC considered that the substitution of ticagrelor and clopidogrel would not be proportional to the PBS utilisation statistics. The ESC considered that prasugrel will most likely substitute for clopidogrel and that ticagrelor will be preferred over prasugrel (see paragraph 4.6).
- The assumption that all patients will receive one year of treatment was inconsistent with data from the 2016 DUSC analysis of predicted versus actual utilisation of ticagrelor which indicated that approximately 50% of patients discontinue ticagrelor treatment within the first 12 months, 30% discontinue treatment between Years 1 and 2, and 20% of patients continue treatment beyond Year 2.

- The submission's estimate of the incidence of ACS includes fatal events, which would overestimate the eligible population. Further, the assumption that the incidence of ACS will be constant over the first 6 years of listing was inconsistent with data from AIHW which indicates that ACS event rates have been declining over time.
- The estimates do not account for 60-day prescribing for ticagrelor, clopidogrel, and clopidogrel with aspirin.

6.60 Overall, the net financial implications to the PBS/RPBS will be dependent on the proportion of substitution from the more expensive ticagrelor versus the less expensive clopidogrel, and the extent to which prasugrel will substitute for clopidogrel use that is below general patient copayment. As noted, the ESC considered that prasugrel will most likely substitute for clopidogrel rather than ticagrelor.

For more detail on PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend prasugrel, in combination with aspirin, for the treatment of acute coronary syndrome (ACS) i.e., myocardial infarction (MI) or unstable angina, managed by percutaneous coronary intervention (PCI). The PBAC considered that there was a low clinical need for prasugrel. The PBAC noted that the submission presented a comparison between prasugrel and ticagrelor, with clopidogrel nominated as a secondary comparator; however, the PBAC considered that both ticagrelor and clopidogrel were relevant comparators. The PBAC considered the clinical claim that prasugrel was superior compared to ticagrelor in terms of efficacy was not reasonable, instead considering that prasugrel was non-inferior compared to ticagrelor, but that the claim of non-inferior safety was reasonable. The PBAC recalled that it had previously considered that the superior comparative clinical benefit of prasugrel over clopidogrel, in terms of reduced non-fatal MI events, marginally outweighed the inferior comparative safety profile in terms of a higher incidence of adverse bleeding events. Given that the claim of superior efficacy compared to ticagrelor was not accepted and noting the numerous errors and issues with the economic evaluation, the PBAC considered that the model comparing prasugrel with ticagrelor was unreliable for decision making.
- 7.2 The primary reason for this decision was clinical need.
- 7.3 The PBAC noted that prasugrel, in combination with aspirin, was previously listed on the PBS, but was delisted in July 2020 due to low uptake.
- 7.4 The PBAC noted that the treatment of ACS is protocol driven and that, unlike clopidogrel or ticagrelor, which have a broad ACS indication, prasugrel cannot be given in a number of situations, including to patients who have had a stroke or transient ischemic attack or to patients who do not receive a PCI (see paragraph 4.6 for further detail). Further, the PBAC noted that prasugrel requires dose adjustments for patients aged over 75 years or who weigh less than 60 kg.

- 7.5 The PBAC noted that the proposed restriction allowed patients in whom a PCI was planned, but not performed, to continue to receive prasugrel. The PBAC noted that this was inconsistent with the clinical trial data and the registered TGA indication and advised that prasugrel should be ceased in patients who do not receive a PCI.
- 7.6 The PBAC noted that the submission nominated ticagrelor, in combination with aspirin, as the comparator based on guideline consensus and that clopidogrel, also in combination with aspirin, was nominated as a secondary comparator. However, the PBAC considered, given the limited role of prasugrel in ACS and as the submissions claim that prasugrel was superior in terms of efficacy compared to ticagrelor was not accepted (see paragraph 7.10), that ticagrelor would be the preferred treatment option and would rarely be replaced by prasugrel. In clinical practice the PBAC considered that prasugrel was more likely to replace clopidogrel as the PBAC has previously determined that prasugrel was superior in terms of efficacy compared to clopidogrel. Thus, the PBAC considered that both ticagrelor and clopidogrel were relevant comparators.
- 7.7 The PBAC noted that the comparison with ticagrelor was based on one open-label, randomised controlled trial, ISAR-REACT 5, that compared prasugrel to ticagrelor. The PBAC noted that a number of potentially relevant trials were not identified in the submission's literature review, including a NICE Evidence Review of dual antiplatelet therapy in ACS (2020).
- 7.8 The PBAC noted that although prasugrel was associated with a lower rate of death from any cause, MI or stroke at 1 year compared to ticagrelor (HR = 1.36; 95% CI: 1.09, 1.70), the results were uncertain as:
- 20.4% of patients in each arm of the trial were discharged from hospital without their allocated treatment, including 9.2% of patients in the prasugrel arm and 8.5% in the ticagrelor arm who did not have confirmation of an ACS diagnosis;
 - 9.9% of prasugrel patients and 12.1% of ticagrelor patients discontinued treatment post-discharge; and
 - There was no significant difference between treatments in an 'on treatment' analysis in which the occurrence of the primary endpoint was assessed in a subset of patients discharged on their study medication in the period from hospital discharge to discontinuation of treatment or end of follow-up (HR = 1.34; 95% CI: 0.98, 1.82).
- 7.9 The PBAC noted that the results of the NICE Evidence Review were inconclusive, with the pairwise meta-analysis indicating that at 30 days and 1-year prasugrel was associated with a lower risk of MI compared to ticagrelor and clopidogrel; whereas the network meta-analysis found at 30 days that, although prasugrel may be more effective in terms of reducing all-cause mortality, it was less effective than ticagrelor in terms of reducing MI events. It was noted however, the NICE Evidence Review stated that a network analysis of 1-year outcomes was not appropriate due to inconsistencies between the direct and indirect estimates of treatment effect. The

PBAC considered that the 30-day outcomes had little relevance to the submission and that 1-year outcomes would have been more informative.

- 7.10 Overall, the PBAC rejected the submission's claim that prasugrel was superior to ticagrelor in terms of efficacy. Instead, the PBAC considered that prasugrel was likely non-inferior compared to ticagrelor.
- 7.11 In terms of safety, the PBAC noted that limited data were presented from the ISAR-REACT 5 trial. The PBAC noted that there was no statistically significant difference in the incidence of major bleeding between ticagrelor and prasugrel (HR = 1.12; 95% CI: 0.83, 1.51). Overall, the PBAC considered that the claim that prasugrel was likely to be non-inferior compared to ticagrelor in terms of safety was reasonable.
- 7.12 The submission also presented two trials comparing prasugrel with clopidogrel, TRITON-TIMI 38 and ELDERLY-ACS II. The submission did not provide a clinical claim for the comparison of prasugrel to clopidogrel. However, it was noted that in 2009, based on the results of the TRITON-TIMI 38 trial, the PBAC had accepted that the superior comparative clinical benefit of prasugrel over clopidogrel, in terms of reduced non-fatal MI events, marginally outweighed the inferior comparative safety profile in terms of a higher incidence of adverse bleeding events (Section 12, prasugrel PSD, July 2009 PBAC meeting). The PBAC agreed with ESC that this remained reasonable.
- 7.13 The PBAC noted the submission presented a modelled economic evaluation of prasugrel versus ticagrelor in patients with ACS who are indicated for PCI. The PBAC noted there were numerous errors and issues with the modelled evaluation, and overall considered the model was uninformative as the claim of superior efficacy was not accepted. The PBAC considered a cost minimisation approach (CMA) would be consistent with a claim non-inferior efficacy.
- 7.14 The PBAC noted that the estimated financial impact of listing prasugrel was relatively small due to low uptake rates applied and as it was assumed that the majority of use would replace ticagrelor. The PBAC considered that prasugrel would primarily substitute for the less expensive clopidogrel over ticagrelor, and that the uptake would be lower than estimated in the submission.
- 7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for prasugrel using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- A CMA between prasugrel and clopidogrel incorporating drug costs only. The PBAC acknowledged that a marginal benefit of prasugrel over clopidogrel was previously accepted (see paragraph 7.12); however, in the context of an early re-entry submission, a CMA was appropriate.
 - A CMA between prasugrel and ticagrelor incorporating drug costs only (see paragraph 7.13).
 - Weighting of the above analyses based on expected replacement of clopidogrel

and ticagrelor in clinical practice. The PBAC considered that a weighting of 50% clopidogrel use and 50% ticagrelor use would be pragmatic, given the proportions of use in this population are unknown;

- Revised financial impact estimates addressing the issues outlined in paragraph 7.14 and the cost minimised price based on the above; and
- A revised restriction in which prasugrel is ceased if a PCI is not performed.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Generic Health appreciates the opportunity to resubmit via the early re-entry pathway and is committed to working with the PBAC to bring Prasugrel to Australians in a timely manner for the treatment of ACS (myocardial infarction or unstable angina) managed by percutaneous coronary intervention, in combination with aspirin.