Ticagrelor

for preventing thrombotic events in adults with acute coronary syndromes

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Ticagrelor 90 mg tablet for preventing thrombotic events (cardiovascular death, myocardial infarction and stroke) in adults with acute coronary syndromes, that is, people:
  - with ST-segment-elevation myocardial infarction (STEMI); or
  - with non-ST-segment-elevation myocardial infarction (NSTEMI); or
  - with unstable angina requiring hospitalisation—defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the following characteristics:
    - age 60 years and older;
    - previous myocardial infarction;
    - previous coronary artery bypass grafting (CABG);
    - coronary artery disease with stenosis of 50% or more in at least two vessels;
    - previous ischaemic stroke;
    - previous transient ischaemic attack;
    - carotid stenosis of at least 50%;
    - cerebral revascularisation;
    - diabetes mellitus;
    - peripheral arterial disease; or
    - chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73m^2 of body surface area.

Ticagrelor should be used in combination with low-dose aspirin for up to 12 months.

Subsidy status

Ticagrelor 90 mg tablet is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications. MAF assistance **does not** apply to the ticagrelor 60 mg tablet.

Update published on 2 January 2019

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of ticagrelor for preventing thrombotic events in patients with acute coronary syndromes (ACS) in August 2017. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for ticagrelor was considered in line with the registered indication, and for patient subgroups who have a high unmet need (such as patients whose condition has had an inadequate response to clopidogrel).

1.2 The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money)—the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

1.4 The manufacturer of ticagrelor, which was not recommended for subsidy in 2017 because of unacceptable cost-effectiveness, was invited to submit a revised price proposal, which the Committee considered in August 2018.

Clinical need

2.1 Dual anti-platelet therapy with a $P2Y_{12}$-receptor antagonist (such as ticagrelor or clopidogrel) in combination with maintenance low-dose aspirin for at least 12 months is considered by local cardiologists as the standard of care for ACS, in line with recommendations from international clinical practice guidelines.

2.2 Local clinical experts advised that patients with subsequent episodes of ACS despite compliance with dual anti-platelet therapy of aspirin plus clopidogrel are likely to be resistant to clopidogrel, and would particularly benefit from receiving ticagrelor instead. However, the Committee acknowledged there was limited evidence supporting using ticagrelor in this patient population and agreed the evaluation should consider the use of ticagrelor in line with its registered indication.

Clinical effectiveness and safety

3.1 The Committee agreed that clopidogrel, which is listed on the MOH Standard Drug List (SDL), was the appropriate comparator for ticagrelor when used to prevent thrombotic events in patients with ACS.

3.2 The Committee noted the pivotal trial PLATO showed that:

- Ticagrelor plus aspirin significantly reduced the composite primary endpoint of death from vascular causes, myocardial infarction (MI), or stroke in patients with ACS compared with clopidogrel plus aspirin;
- No significant difference between ticagrelor and clopidogrel in the rates of major bleeding, the primary safety endpoint, was shown. However, ticagrelor was associated with significantly more major bleeding not related to coronary artery bypass grafting; and
- In a retrospective subgroup analysis comprising Asian patients enrolled in the pivotal trial, consistency of efficacy and safety outcomes was observed compared to non-Asian patients.

3.3 The Committee acknowledged that the reduction in cardiovascular events, as measured by the primary composite endpoint, was driven by a reduction in the rates of MI and death from vascular causes but not by stroke.

3.4 The Committee acknowledged there was large variation in the diagnosis of unstable angina within local clinical practice, as it is a highly heterogeneous condition. To ensure appropriate use of ticagrelor, the Committee advised that if an MAF listing was recommended, eligible patients with unstable angina would need to meet specific clinical criteria.

Cost effectiveness

4.1 The Committee considered the cost-effectiveness of ticagrelor from published studies and noted there were two local economic evaluations available in Singapore. Both studies showed that when compared with clopidogrel, ticagrelor was associated with incremental cost-effectiveness ratios (ICERs) of SG$10,136 and SG$18,647 per quality-adjusted life year gained.

4.2 The Committee acknowledged that the magnitude of the reduction in cardiovascular outcomes and the time horizon of the analysis were key drivers of the ICER, and that the true ICER was associated with moderate uncertainty and could be higher than reported. They also noted that compared with generic clopidogrel, ticagrelor was unlikely to represent a cost-effective alternative even at the discounted price proposed by the manufacturer through value-based pricing (VBP) discussions in 2017.

4.3 Following a revised price proposal from the manufacturer for ticagrelor in 2018, the Committee agreed the revised cost was reasonable and could be considered as an acceptable use of healthcare resources.

Estimated annual technology cost

5.1 The Committee estimated that around 2,200 people with ACS in Singapore would benefit from government assistance for ticagrelor. The annual cost impact was estimated to be between SG$1 million to SG$3 million in the first year of listing on the MAF.

5.2 The Committee noted the annual subvention amount was expected to increase year-on-year because of the ageing population and increasing incidence of ACS in Singapore.

Additional considerations

6.1 In August 2017, the Committee acknowledged that existing PAPs implemented at several public healthcare institutions in Singapore effectively reduced the cost of ticagrelor to lower than the price proposed by the manufacturer for subsidy consideration.

6.2 At that time, the Committee was aware that patients not eligible for MAF would be at risk of paying more for ticagrelor if it was listed on MAF, since the manufacturer would no longer support PAPs once subsidy was available.

6.3 However, in August 2018, the Committee acknowledged that the manufacturer had addressed their previous concerns and offered an acceptable revised cost price.

Recommendation

7.1 Based on evidence presented in August 2017, the Committee did not recommend ticagrelor 90 mg tablet for inclusion on the MAF for preventing thrombotic events in patients with ACS as it was unlikely to reflect a cost-effective use of healthcare resources at the price proposed by the manufacturer at that time, which was also higher than existing PAPs.

7.2 In August 2018, following an acceptable revised price proposal from the manufacturer, the Committee recommended ticagrelor 90mg tablet for listing on the MAF for preventing thrombotic events in adults with ACS who meet certain clinical criteria.

VERSION HISTORY

Guidance on ticagrelor for preventing thrombotic events in adults with acute coronary syndromes

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**
   Date of Publication 5 February 2018

2. **Guidance updated to extend MAF listing to ticagrelor**
   Date of Publication 2 January 2019

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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