Trastuzumab

for the treatment of metastatic breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

✓ Trastuzumab 440mg IV formulation for the treatment of HER2-positive metastatic breast cancer in the following circumstances:
  - In combination with a taxane for patients who have not received chemotherapy for their metastatic disease, or
  - In combination with an aromatase inhibitor for postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

Patients must have evidence of HER2 gene amplification as demonstrated by immunohistochemistry or fluorescence in situ hybridisation (FISH) either in the primary tumour or a metastatic lesion.

Trastuzumab should be discontinued at disease progression.

Trastuzumab must not be used in patients with a left ventricular ejection fraction (LVEF) of less than 50% or with symptomatic heart failure.

Subsidy status

Trastuzumab 440mg IV formulation is recommended for inclusion on the Medication Assistance Fund (MAF) in line with the abovementioned criteria.

MAF only applies to the first 8 cycles of IV trastuzumab, or until disease progression, whichever occurs first.

MAF does not apply to trastuzumab 600mg subcutaneous formulation.

Grandfathered patients

Patients who are eligible for MAF, who are currently receiving IV trastuzumab for HER2-positive metastatic breast cancer, and whose disease has not progressed while on treatment, can use MAF for IV trastuzumab for up to a total of 8 cycles*, or until disease progression, whichever occurs soonest.

* The total number of cycles eligible for MAF is calculated by subtracting any cycles which were administered before MAF listing was implemented in May 2017.
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 trastuzumab (both intravenous and subcutaneous formulations) for the treatment of metastatic breast cancer. The Agency for Care Effectiveness conducted the evaluation, and reviewed evidence dossiers submitted by the manufacturer, in consultation with the Oncology Drug Subcommittee (ODS) of the MOH Drug Advisory Committee and the MOH Breast Cancer Working Group members.

1.2 The evaluation focused on the use of trastuzumab in combination with paclitaxel (or docetaxel) as a first-line treatment for patients who have not received chemotherapy for metastatic breast cancer, as this indication currently constitutes about 90% of trastuzumab use in the metastatic setting in Singapore. A summary of published clinical and economic evidence relating to the use of trastuzumab in combination with an aromatase inhibitor in post-menopausal women, or as second-line monotherapy was also considered by the Committee to inform deliberations on the appropriate use of trastuzumab for the additional registered indications in metastatic breast cancer.

1.3 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
   - Estimated annual technology cost and the number of patients likely to benefit from the technology.

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

Clinical need

2.1 The Committee recognised that trastuzumab is listed as an essential medicine by the World Health Organization and considered by clinicians as the gold-standard first-line treatment for patients with metastatic breast cancer in Singapore. Almost all eligible patients have been receiving trastuzumab since it was made commercially available in 1999.
Clinical effectiveness and safety

3.1 The Committee agreed that the addition of IV trastuzumab to taxane-containing regimens (either paclitaxel or docetaxel) for the treatment of metastatic breast cancer statistically significantly improved overall survival and overall response rates, and reduced the risk of disease progression compared with taxane monotherapy.

3.2 The Committee acknowledged that there was limited evidence to support the use of trastuzumab beyond disease progression, or to determine the optimal duration of treatment in the metastatic setting.

3.3 The Committee also acknowledged that clinical evidence supporting the use of subcutaneous trastuzumab was derived from trials conducted in early breast cancer only. While results showed that the pharmacokinetic profile, efficacy (response rate) and safety of the subcutaneous formulation was statistically non-inferior to the IV preparation, numerically more serious adverse events occurred in the subcutaneous group compared to the IV group.

3.4 The Committee considered the evidence to support the use of trastuzumab in combination with an aromatase inhibitor in post-menopausal women for metastatic breast cancer, and accepted that it was limited. It concurred with the ODS’s advice that an MAF listing for use in this setting was appropriate given the low number of patients currently receiving this treatment regimen (about 8% of trastuzumab use) and high unmet need.

3.5 In the absence of comparative analyses, the Committee agreed that there was considerable uncertainty about the effectiveness of trastuzumab monotherapy (for second- or subsequent-line treatment of metastatic breast cancer) and results should be interpreted with caution. The Committee concurred with the ODS’s view that it did not consider that trastuzumab monotherapy should be recommended for MAF subsidy, as newer agents have replaced trastuzumab in this setting and the number of patients eligible for treatment each year would be very small.

3.6 The Committee considered the safety profile of trastuzumab and acknowledged the increased risk of cardiotoxicity associated with use reported in the pivotal trials. It concurred with advice from the ODS and the MOH Breast Cancer Working Group that trastuzumab should not be used in patients with a left ventricular ejection fraction of less than 50% or with symptomatic heart failure.
Cost effectiveness

4.1 In the manufacturer’s base-case analyses, the incremental cost-effectiveness ratio (ICER) was considerably higher than what is usually considered cost-effective. The ACE technical team conducted a series of scenario analyses using the manufacturer’s cost-effectiveness model to determine the impact on the ICER of stopping treatment at disease progression, or only subsidising a specific number of treatment cycles.

4.2 The Committee noted from ACE’s analyses that if trastuzumab was only subsidised until disease progression, or capped at a specific number of treatment cycles, the manufacturer’s base case ICER improved substantially. The Committee acknowledged that if subsidy was only given for 8 cycles at a selling price of XXXX*, the manufacturer’s base case ICER fell within the range of $45,000 to $75,000 per QALY gained, and could be considered an acceptable use of healthcare resources. ICERs for the subcutaneous formulation were of a similar magnitude.

* Information redacted

4.3 The Committee agreed with the ODS and the MOH Breast Cancer Working Group that since clinicians were unable to define disease progression in clinical practice using a standardised approach, the most feasible way to ensure the cost-effective use of trastuzumab was to restrict the number of cycles subsidised.

4.4 The Committee heard that the ODS advised that a grandfathering recommendation should also be considered to support existing patients receiving trastuzumab. The Committee supported this recommendation on grounds of equity and recommended that patients who have not completed 8 cycles of treatment and whose disease has not progressed would be eligible for MAF for a maximum of 8 cycles, calculated by taking into account the cycles that had already been administered before MAF is applied (from 3 May 2017). For example, a patient who has had 3 cycles of trastuzumab for metastatic breast cancer before the MAF listing is implemented, will be eligible to receive MAF for a maximum of 5 cycles, or until disease progression, whichever occurs earlier.
Estimated annual technology cost

5.1 The Committee estimated that around 100 people in Singapore would benefit from Government assistance for IV trastuzumab. The cost impact varied considerably depending on the number of cycles subsidised. Hence, to provide greater certainty on the cost to Government, the Committee agreed to recommend MAF for up to 8 cycles. The annual cost to the MAF at the current price was estimated to fall in the range of $1 to $3 million per year in the near term.

5.2 Assistance for grandfathered patients only applies in the first year of the MAF listing, and is estimated to have a low cost impact.

Additional considerations

6.1 The Committee considered that listing the subcutaneous formulation of trastuzumab on the MAF would drive switching and could limit the potential cost savings available when IV biosimilars enter the market, as most patients and clinicians would be reluctant to switch back to an IV formulation. The Committee agreed that MAF should not apply to the subcutaneous formulation of trastuzumab at its current price.

Recommendation

7.1 The Committee recommended IV trastuzumab 440mg for listing on the MAF in combination with a taxane or aromatase inhibitor for patients with metastatic breast cancer who meet certain clinical conditions, on the basis of its significant improvement in overall survival and response rates compared to taxane monotherapy.

7.2 In the absence of sufficient evidence to support the use of trastuzumab beyond disease progression, and unacceptable cost-effectiveness beyond 8 cycles of treatment at the price proposed by the manufacturer, the Committee recommended that MAF subsidy should be restricted to up to 8 cycles or until disease progression, whichever occurs soonest.

7.3 Trastuzumab 600mg subcutaneous formulation was not recommended for listing on the MAF at its proposed price, due to its potential impact on downstream cost savings that are anticipated following biosimilar entry.
VERSION HISTORY

Guidance on trastuzumab for metastatic breast cancer

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 3 May 2017

2. **Amendment to redact cost information**
   Date of Publication 5 Feb 2018