Technology Guidance

Osimertinib

for treating EGFR mutation-positive non-small-cell lung cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Osimertinib 40 mg and 80 mg tablets for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) in patients whose disease has progressed on or after EGFR TKI therapy. For patients with isolated brain metastases who are clinically ineligible for re-biopsy and where T790M cannot be confirmed, osimertinib may be used until progression.

Subsidy status

Osimertinib 40 mg and 80 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

MAF assistance **does not** apply to osimertinib 40 mg or 80 mg tablets when used for adjuvant treatment of EGFR mutation-positive NSCLC after tumour resection, or for newly diagnosed locally advanced or metastatic EGFR mutation-positive NSCLC.

Clinical indications, subsidy class and MediShield Life claim limits for osimertinib are provided in the Annex.

Published: 12 July 2022

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 osimertinib for treating epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for osimertinib was considered in line with its registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of osimertinib and provided clinical advice on its appropriate and effective use based on the available clinical evidence.

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.

Clinical need

2.1. The Committee noted that approximately 350 patients are diagnosed with EGFR mutation-positive advanced NSCLC each year in Singapore and there was a clinical need to consider osimertinib and other tyrosine kinase inhibitors (TKIs) for subsidy to improve treatment affordability and ensure appropriate patient care.

2.2. <u>Adjuvant treatment following tumour resection</u>
The Committee acknowledged that chemotherapy is the standard of care for adjuvant treatment following tumour resection in NSCLC, with overall survival (OS) benefit shown at 5 years. Although osimertinib is the only TKI approved for adjuvant treatment in patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R mutations, the Committee noted that it is not routinely used in local practice because data confirming its OS benefits are still immature.

2.3. Newly diagnosed advanced EGFR mutation-positive NSCLC

In local clinical practice, TKIs are standard of care for treating newly diagnosed, advanced EGFR mutation-positive NSCLC, in line with international clinical practice guidelines. All patients with non-squamous NSCLC are routinely tested for the presence of oncogenic markers prior to starting treatment, and up to 60% of patients in Singapore have EGFR mutations. The Committee acknowledged that afatinib, dacomitinib, erlotinib and gefitinib are included in the MOH List of Subsidised Drugs for treating EGFR mutation-positive NSCLC.[1,2]

2.4. Advanced EGFR T790M mutation-positive NSCLC after disease progression

The Committee heard from the clinical experts that 50-60% of patients with EGFR mutation-positive NSCLC develop a T790M mutation while receiving a first or second generation TKI and will require treatment with osimertinib. For patients who have already received osimertinib in the first-line setting, or who do not have a T790M mutation, chemotherapy is considered.

Clinical effectiveness and safety

3.1. Adjuvant treatment following tumour resection

The Committee reviewed the available clinical evidence (ADUARA trial) that showed osimertinib was superior to placebo for the surrogate endpoint of disease-free survival. The planned treatment duration was 3 years. However, the trial results were released 2 years early, and OS data was immature. The Committee concluded that it was not certain to what extent a benefit in disease-free survival would translate into a benefit in OS.

3.2. Newly diagnosed advanced EGFR mutation-positive NSCLC

The Committee reviewed the available clinical evidence (FLAURA) and noted that osimertinib led to statistically significantly longer OS and PFS gains compared to first generation TKIs (erlotinib or gefitinib). Osimertinib also led to numerically fewer cases of central nervous system (CNS) metastasis.

3.3. The Committee noted that FLAURA showed no significant differences in OS when analyses were conducted in the Asian subgroup (hazard ratio between osimertinib and erlotinib/gefitinib = 1.00, 95%CI 0.75 to 1.32). Conversely in the non-Asian subgroup, the hazard ratio was 0.54, 95%CI 0.38 to 0.77.

3.4. The Committee noted that there was no head-to-head randomised controlled trial comparing osimertinib with afatinib or dacomitinib. Results from indirect evidence considered by NICE (UK) suggested that dacomitinib and afatinib were comparable in clinical efficacy, and osimertinib was associated with longer PFS compared with

[1] ACE Technology guidance for dacomitinib for treating EGFR mutation-positive NSCLC
[2] Update of MOH List of Subsidised Drugs to include treatments for various cancer conditions

afatinib; however, the Committee acknowledged that NICE did not conduct a comparison of dacomitinib versus osimertinib.

3.5. Advanced EGFR T790M mutation-positive NSCLC after disease progression
The Committee reviewed the available clinical evidence (AURA3) comparing osimertinib with platinum-based chemotherapy in patients with advanced EGFR T790M mutation-positive NSCLC that had progressed on or after treatment with an EGFR TKI. Results showed that osimertinib led to statistically longer PFS. However, no statistically significant difference was observed between the treatment arms at the final OS analysis, at which time 71% of patients randomised to chemotherapy had crossed over to osimertinib treatment. Osimertinib was associated with less grade ≥3 toxicity compared with chemotherapy.

Cost effectiveness

4.1. The manufacturer of osimertinib was invited to submit value-based pricing (VBP) proposal for subsidy consideration. The Committee acknowledged that the prices proposed for osimertinib in various listing scenarios were considerably higher than all other available TKIs.

4.2. Adjuvant treatment following tumour resection
No published local cost-effectiveness studies of osimertinib for adjuvant treatment were identified; however, the Committee noted a study presented at the 2021 ASCO Annual Meeting that reported an incremental cost effectiveness ratio (ICER) of US$317,120 per QALY gained when osimertinib was used as adjuvant treatment for stage IB to IIIA NSCLC. Given the uncertain OS benefit, the Committee acknowledged that osimertinib was unlikely to represent a cost-effective use of healthcare resources at the price proposed by the manufacturer.

4.3. Newly diagnosed advanced EGFR mutation-positive NSCLC
The Committee reviewed an in-house cost effectiveness analysis conducted by ACE of osimertinib versus first generation TKIs (erlotinib or gefitinib) in patients with newly diagnosed advanced EGFR mutation-positive NSCLC. Osimertinib was associated with a base-case ICER of more than SG$105,000 per QALY gained compared with erlotinib or gefitinib. The Committee noted that the analysis was conducted using the survival curves (with OS gains for osimertinib) from the overall population in the FLAURA study. However, the ICER in the local setting was likely to be underestimated given the potential lack of OS benefit in the Asian subgroup. The ICER was also expected to increase further after taking into consideration generic prices for erlotinib and gefitinib. In addition, the cost of osimertinib is much higher than afatinib and dacomitinib. In view of the results, the Committee agreed that osimertinib was unlikely to represent a cost-effective treatment option for newly diagnosed disease compared to the other TKIs.

4.4. Advanced EGFR T790M mutation-positive NSCLC after disease progression

In the absence of a local cost-effectiveness analysis, the Committee reviewed evaluations from overseas HTA agencies, which had reimbursed osimertinib for this indication, and agreed that the results were likely to be generalisable to the local context. The Committee agreed that patients whose disease has progressed after EGFR TKIs had limited treatment options and a poor prognosis, therefore, there was a high clinical need to provide them with a subsidised treatment.

Estimated annual technology cost

5.1. Adjuvant treatment following tumour resection

The Committee noted that the annual cost impact for osimertinib was estimated to be between SG$5 million to less than SG$10 million in the first year of listing based on local epidemiological rates. They acknowledged that there was uncertainty surrounding the cost estimates as the average treatment duration in local practice was likely to be longer than what has been observed in trial settings to date.

5.2. Advanced EGFR mutation-positive NSCLC

Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact for osimertinib in the first year of listing on the MAF was estimated to be:

- more than SG$10 million for treating newly diagnosed, advanced EGFR mutation-positive NSCLC; and
- between SG$5 million to less than SG$10 million for treating advanced EGFR T790M mutation-positive NSCLC after disease progression.

Additional considerations

6.1. The Committee acknowledged that, contingent on a subsidy listing, the manufacturer agreed to implement a patient assistance programme (PAP) for osimertinib in the public healthcare institutions which would provide further savings to eligible patients in addition to MAF financial assistance.

Recommendation

7.1 Adjuvant treatment of EGFR mutation-positive NSCLC following tumour resection

Based on available evidence, the Committee recommended not listing osimertinib on the MAF for adjuvant treatment of EGFR mutation-positive NSCLC following tumour resection, in view of uncertain clinical benefit and cost-effectiveness at the price proposed by the manufacturer.

7.2 Treatment of advanced EGFR mutation-positive NSCLC

At the price proposed by the manufacturer, osimertinib was not recommended for listing on MAF for newly diagnosed EGFR mutation-positive NSCLC due to unacceptable cost effectiveness compared with the other EGFR TKIs.

7.3 The Committee recommended osimertinib 40 mg and 80 mg tablets be listed on MAF for treating patients with advanced EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy, given its acceptable cost effectiveness compared with chemotherapy, and the high clinical need to ensure appropriate patient care.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Osimertinib 40 mg and 80 mg tablets	Adjuvant treatment after tumour resection in patients with stage IB to IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Treatment should be continued until disease recurrence or unacceptable toxicity or a maximum of 3 years.	Not recommended for subsidy	$2400 (1 September 2022)
Osimertinib 40 mg and 80 mg tablets	For newly diagnosed locally advanced or metastatic EGFR mutation-positive NSCLC, including patients who have developed intolerance to another EGFR tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal.*	Not recommended for subsidy	$2400 (1 September 2022)
Osimertinib 40 mg and 80 mg tablets	Treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy. For patients with isolated brain metastases who are clinically ineligible for re-biopsy and where T790M cannot	MAF	$2400 (1 September 2022)

	be confirmed, osimertinib may be used until progression.		

Abbreviation: MAF, Medication Assistance Fund; NSCLC, non-small-cell lung cancer.
*revised clinical indication with effect from 1 Mar 2024.

VERSION HISTORY

Guidance on osimertinib for treating EGFR mutation-positive non-small-cell lung 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 12 July 2022

2. **Guidance updated to reflect updated clinical criteria for treatment of locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy**

   Date of Publication 1 June 2023

3. **Guidance updated to reflect updated clinical criteria for treatment of newly diagnosed locally advanced or metastatic EGFR mutation-positive NSCLC**

   Date of Publication 1 February 2024

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. 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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