# Osimertinib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01EB04

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| **Indication** | Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C25.Y |
| **INN** | Osimertinib |
| **Medicine type** | Chemical agent |
| **List type** | Complementary |
| **Formulations** | **Oral > Solid:** 40 mg (as mesylate) ; 80 mg (as mesylate) |
| **EML status history** | Application rejected in 2021 (TRS 1035)<br>Application rejected in 2023 (TRS 1049) |
| **Sex** | All |
| **Age** | Adolescents and adults |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org<br>Read more about patents. |
| **Tags** | Cancer |
| **Wikipedia** | Osimertinib |
| **DrugBank** | Osimertinib |

## Expert Committee recommendation

The Expert Committee once again recognized the public health importance of effective and safe treatments for lung cancer, a disease that has a high global burden. The Committee recalled that osimertinib was not recommended for inclusion on the EML in 2021, despite promising data from the FLAURA trial showing osimertinib to be associated with extended overall survival compared with earlier generation EGFR tyrosine kinase inhibitors already included on the EML. The 2021 Committee considered the data at the time were still immature and had serious concerns about the high price of osimertinib and lack of cost–effectiveness compared with older generation tyrosine kinase inhibitors listed on the EML for NSCLC, which are more affordable because of the availability of generic products. The Committee noted that the current data, after a median of 35.8- and 27.0-month follow-up in the osimertinib and comparator arms, respectively, showed a median overall survival gain of 6.8 months for osimertinib, which met the established threshold for EML consideration. However, the Committee noted again the high price of osimertinib compared with older generation tyrosine kinase inhibitors in most countries, but particularly in low- and middle-income countries. Consequently, the Committee was concerned that recommending the inclusion of osimertinib on the EML could worsen health inequity by diverting limited resources away from less expensive medicines already listed on the EML for this indication. Furthermore, the Committee

noted the input from the EML Cancer Medicines Working Group on a phase III trial comparing gefitinib in combination with chemotherapy to gefitinib monotherapy. The trial found that the addition of chemotherapy to the first-generation tyrosine kinase inhibitor significantly improved overall survival, to a magnitude similar to that associated with the use of osimertinib, albeit with a higher risk of toxicity. The Committee considered that this approach to treatment, using medicines already included on the EML, may be a more feasible, affordable and equitable option at this time, particularly in resource-constrained settings. The Expert Committee therefore did not recommend addition of osimertinib to the complementary list of the EML for the first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC. The Committee recommended that data for osimertinib continue to be evaluated as they evolve and encouraged efforts to facilitate affordable access to osimertinib in low- and middle-income settings, for example, by negotiating public health licensing agreements through the Medicines Patent Pool.

## Background

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor. It was previously considered for inclusion on the EML by the Expert Committee in 2021 but was not recommended because of concerns about the clinical benefit and comparative cost–effectiveness. The Expert Committee noted that the application to list osimertinib was based on the results of a single randomized control trial (FLAURA) in which overall survival data were immature. Therefore, the efficacy of osimertinib compared with erlotinib and gefitinib was uncertain. Furthermore, the Committee was concerned about the high price of osimertinib and several analyses had concluded that osimertinib was not cost-effective at common willingness-to-pay thresholds. At the time, the Committee considered listing osimertinib as a therapeutic alternative to the EGFR tyrosine kinase inhibitors included on the EML. However, given the difference in prices between the medicines, the Committee decided against this option because of the considerable additional expenditure it would impose at the country level (1).

## Public health relevance

Lung cancer is the most diagnosed and leading cause of death from cancer worldwide, with more than 2 million new cases and almost 1.8 million deaths in 2020 (2). Lung cancer is a highly lethal malignancy, with an economic burden estimated at around US$ 8 billion in productivity loss in the BRICS countries – Brazil, Russia, India, China and South Africa (3). More than 80% of lung cancers are classified as non-small cell (4), and about 70% are diagnosed at advanced or metastatic stages, with large regional variation (3, 5, 6). Targeted therapies have changed the therapeutic landscape for patients with NSCLC that is molecularly druggable (e.g. EGFR mutations, anaplastic lymphoma kinase rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements and BRAF mutations) in metastatic disease. However, these therapies are ineffective in most patients with NSCLC who have tumours that lack such genetic alterations (7). The overall prevalence of EGFR mutations has been reported as about 30%, although this varies by world region, risk factors and population phenotype. For instance, the Asian-Pacific region has the highest prevalence of EGFR mutations (47%), followed by South America (36%), North America (22%), Africa (21%), Europe (15%) and Oceania (12%) (8-–10).

## Benefits

The FLAURA trial was a phase III, double-blind, clinical trial (556 participants) that compared osimertinib with gefitinib and erlotinib for first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC (11, 12). Participants were randomized in a 1:1 ratio to receive osimertinib 80 mg once daily, or standard treatment (gefitinib 250 mg once daily or erlotinib 150 mg once daily) until disease progression, unacceptable toxicity or withdrawal of consent. At the time of the primary analysis for the primary endpoint of progression-free survival, osimertinib was associated with a statistically significant improvement compared with standard treatment (median progression-free survival 18.9 months versus 10.2 months; hazard ratio (HR) for disease progression or death 0.46, 95% confidence interval (CI) 0.37 to 0.57). Osimertinib also demonstrated a significant progression-free survival benefit for participants with central nervous system metastasis, a common site of progression of NSCLC and frequently responsible for deterioration in quality of life (median progression-free survival 15.2 months versus 9.6 months; HR for disease progression or death 0.47, 95% CI 0.30 to 0.74) (11). A final analysis was

performed for the secondary endpoint of overall survival with a median duration of follow-up for overall survival of 35.8 months in the osimertinib group and 27.0 months in the comparator group. Median overall survival favoured the osimertinib group over the standard treatment group (median overall survival 38.6 months versus 31.8 months; HR 0.80, 95% CI 0.64 to 1.00), that is, a 6.8-month survival gain in absolute terms. At 36 months, 54% of participants in the osimertinib group were alive compared with 44% in the comparator group (12). Based on the FLAURA trial, osimertinib received a score of 4 on the magnitude of clinical benefit scale of the European Society for Medical Oncology (13). A 2022 systematic review and meta-analysis of seven randomized controlled trials (3335 participants) evaluated the efficacy and safety of osimertinib in patients with EGFR-mutated NSCLC (14). Pooled efficacy comparisons showed that osimertinib was associated with higher overall response rate (relative risk (RR) 2.42, 95% CI 0.92 to 6.39; three studies), significantly longer progression-free survival (HR 0.28, 95% CI 0.18 to 0.44; four studies) and significantly longer overall survival (HR 0.78, 95% CI 0.68 to 0.97; four studies) versus the comparators (chemotherapy, other EGFR-tyrosine kinase inhibitors, docetaxel plus bevacizumab, and placebo). Given the public health relevance of elderly populations in the treatment of NSCLC, a network meta-analysis of 12 randomized controlled trials (3779 participants) assessed the efficacy of different first-line treatments for EGFR-mutated NSCLC in elderly and non-elderly patients (15). In patients older than 65 years, 12 studies reported progression-free survival and seven studies reported overall survival. For the comparison of osimertinib versus standard of care (first-generation tyrosine kinase inhibitors) plus chemotherapy, no significant differences were seen between treatment arms for progression-free survival (HR 0.87, 95% credible interval (CrI) 0.13 to 7.52; favouring osimertinib) or overall survival (HR 0.95, 95% CrI 0.34 to 2.54; favouring standard of care plus chemotherapy). As central nervous system progression is a special concern due to its frequency and associated morbidity and mortality in metastatic NSCLC patients, a prespecified analysis was conducted in 128 patients from FLAURA trial. The results showed a 2.5 times higher central nervous system overall response rate (66% versus 43%), and a lower central nervous system progression rate of 20% versus 39% in favour of osimertinib compared with first-generation tyrosine kinase inhibitors (16).

## Harms

From evidence presented previously from the FLAURA trial (12), adverse events of grade 3 or higher were reported in 42% and 47% of participants in the osimertinib group and standard treatment group, respectively. The most reported adverse events (any grade) possibly related to osimertinib treatment (investigator assessed) were diarrhoea, rash or acne, paronychia, dry skin, and stomatitis. Serious adverse events were reported in 27% of the participants in each treatment arm. Decreased ejection fraction was reported in a greater proportion of participants in the osimertinib group than the standard treatment group (5% versus 2%). Similarly, QT prolongation was also reported in a greater proportion of participants in the osimertinib group than the standard treatment group (10% versus 4%). Compared with the primary analysis, there were no new reports of interstitial lung disease or pneumonitis, which were both reported in 2% and 1% of participants in the osimertinib and standard treatment groups, respectively. An analysis of patient-reported outcomes of FLAURA trial patients showed similar outcomes for both arms for the safety, toxicity and quality-of-life domains analysed (17). According to FLAURA data, grade 3 or higher adverse event rates were 34% in the osimertinib group and 45% in the comparator group, indicating a better toxicity profile for osimertinib.

## Cost / cost effectiveness

No new cost–effectiveness data were presented in the application beyond those considered in 2021 (18, 19). Osimertinib is generally considered not to be cost-effective in most health care systems at current prices and common willingness-to-pay thresholds. In a 2019 study that compared the cost–effectiveness of treatment strategies for NSCLC, costs per day for osimertinib in China and the United States were US$ 259 (US$ 129–259) and US$ 568 (US$ 284–568), respectively (20).

## WHO guidelines

WHO guidelines for treatment of NSCLC are not available.

## Availability

Osimertinib (manufactured by Astra Zeneca) has primary patent and secondary patent protection until 2032 and 2035, respectively. A generic version is available in Bangladesh.

## Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department advised that it did not support the inclusion of osimertinib on the EML at this time. The technical department acknowledged that osimertinib was associated with clinical benefits when compared with the first-generation tyrosine kinase inhibitors, gefitinib and erlotinib, for overall survival gain, and it had a more favourable toxicity profile. However, first-generation tyrosine kinase inhibitors are already included on the EML and are more cost-effective than osimertinib and have a lower impact on health budgets. The EML Cancer Medicines Working Group reviewed the application and advised that it did not support the inclusion of osimertinib on the EML for first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC. The Working Group noted that the evidence indicated that osimertinib had meaningful overall survival benefit compared with the earlier generation tyrosine kinase inhibitors currently listed on the EML (erlotinib, gefitinib and afatinib) when used as monotherapy. However, the Working Group noted evidence from a randomized, phase III trial comparing gefitinib monotherapy versus gefitinib in combination with chemotherapy (21) in which the addition of chemotherapy to gefitinib significantly prolonged overall survival: not reached versus 17 months (95% CI 13.5 to 20.5 months); HR for death 0.45 (95% CI 0.31 to 0.65). Other trials have shown similar results. The Working Group therefore considered that the benefit of first-generation tyrosine kinase inhibitors in combination with chemotherapies might provide similar benefits to those associated with the use of osimertinib, albeit at a higher risk of toxicity. At the current high price, osimertinib has not been found to be cost-effective and would pose serious affordability challenges, especially in resource-constrained settings. The Working Group also noted the availability of aumolertinib, which received regulatory approval from the Chinese National Medical Products Administration for the treatment of NSCLC patients with EGFR T790M mutations who had progressed on or after other EGFR tyrosine kinase inhibitor therapy. The approval was based on findings from the open-label phase II APOLLO study (22). Additional support for the efficacy of aumolertinib comes from the phase III AENEAS trial, in which progression-free survival was significantly longer with aumolertinib than gefitinib (HR 0.46, 95% CI 0.36 to 0.60) (23).


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