A.23	Osimertinib - EGFR mutated locally advanced or metastatic non-small cell lung cancer.
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Lung cancer is the second most diagnosed and the leading cause of death for cancer worldwide, with an estimated 2,206,771 new cases and 1,796,144 related deaths in 2020, according to GLOBOCAN. The incidence to death ratio speaks to its lethality ,a burden compounded by an estimated economic impact of about $8 billion in productivity lost in the BRICS countries where liver and lung cancer have the largest impact on lost productivity due to their high incidence. Although emerging evidence suggest lung cancer screening may blunt mortality rates, on a global scale an effective screening program is not realistic so that lung cancer diagnoses occur in advanced stages (i.e., III and IV, TNM 8th) in more than 60% of cases, with highly regional variability. Over 80% of the lung cancers are classified as non-small cell (NSCLC), and nearly 70% are diagnosed at late stages as locally advanced or metastatic. Beginning with the demonstration that mutations in the epidermal growth factor receptor (EGFR) could “drive” a fraction of NSCLCs, advances have been made in understanding the molecular underpinnings of an increasing fraction of lung cancers and at the present time in the metastatic setting, 15 to 25 percent of lung cancers are found to harbor alterations that can be considered potentially “druggable” in “oncogenic drivers” including mutations in EGFR (epidermal growth factor receptor, and BRAF (B-rapidly accelerated fibrosarcoma) rearrangements in the anaplastic lymphoma kinase [ALK] and ROS1, mutations or amplifications in HER2 (human epidermal growth factor receptor 2), and fusions in NTRK1-3 (N-tropomyosin receptor kinase). Importantly, although often encumbered by low grade, but chronic toxicities that lead to their discontinuation the novel “targeted therapeutics”, have been shown to provide meaningful clinical benefit and a better toxicity profile when compared to previous standard chemotherapy regimens. In NSCLC, mutations in EGFR are the most prevalent abnormality. A meta-analysis and systematic reviews estimate an overall EGFR mutation prevalence of approximately 30%, although the prevalence of mutations in the EGFR varies according to the world region, risk factors and population phenotype. The present submission concerns osimertinib, a third generation EGFR TKI.

Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	As a membrane receptor with kinase activity mediated by an intracellular domain where a critical tyrosine residue resides, drugs that target epidermal growth factor receptors (EGFR) harboring activating mutations are often referred to as tyrosine kinase inhibitors (TKIs). First- and second-generation tyrosine kinase inhibitors are approved world-wide and the present submission concerns osimertinib, a third generation EGFR TKI. Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits mutations that both sensitize to EGFR TKIs and those that confer resistance (*EGFR* T790M) resistance mutations. The FLAURA trial was a double-blind, phase 3 trial, that randomly assigned 556 patients with previously untreated, advanced non–small-cell lung cancer (NSCLC) harboring *EGFR* exon 19 deletions or EGFR L858R mutations in a 1:1 ratio to receive either 80 osimertinib once daily) or gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily. The primary end point was investigator-assessed progression-free survival. Although the objective response rate was similar with osimertinib (80%) and gefitinib/erlotinib (76%) (odds ratio, 1.27; 95% confidence interval [CI], 0.85 to 1.90; P=0.24), the median progression-free survival (PFS) was significantly longer with osimertinib than with gefitinib/erlotinib (18.9 vs. 10.2 months; hazard ratio (HR), 0.46; 95%CI, 0.37 to 0.57; P<0.001). The median duration of response was 17.2 months (95%CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95%CI, 7.3 to 9.8) with gefitinib/erlotinib. The safety profile was similar. In the first-line treatment of advanced NSCLC harboring EGFR mutations, the authors concluded osimertinib efficacy was superior when compared to gefitinib/erlotinib with a similar safety profile. A subsequent publication reported the median overall survival as 38.6 months (95%CI, 34.5 to 41.8) in the osimertinib group and 31.8 months (95%CI, 26.6 to 36.0) in the gefitinib/erlotinib group (HR 0.80; 95.05%CI, 0.64 to 1.00; P=0.046). At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the gefitinib/erlotinib group were continuing to receive a trial regimen; the median exposure was 20.7 months and 11.5 months, respectively. In this more robust analysis similar rates of grade 3 or higher adverse events of were reported in 42% of the patients in the osimertinib group and in 47% of those in the gefitinib/erlotinib group.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Summarized above for the FLAURA trial a double-blind, phase 3 trial, that randomly assigned 556 patients with previously untreated, advanced non–small-cell lung cancer (NSCLC) harboring *EGFR* exon 19 deletions or EGFR L858R mutations in a 1:1 ratio to receive either 80 osimertinib once daily) or gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily. The primary end point was investigator-assessed progression-free survival. Although the objective response rate was similar with osimertinib (80%) and gefitinib/erlotinib (76%) (odds ratio, 1.27; 95% confidence interval [CI], 0.85 to 1.90; P=0.24), the median progression-free survival (PFS) was significantly longer with osimertinib than with gefitinib/erlotinib (18.9 vs. 10.2 months; hazard ratio (HR), 0.46; 95%CI, 0.37 to 0.57; P<0.001). The median duration of response was 17.2 months (95%CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95%CI, 7.3 to 9.8) with gefitinib/erlotinib. In the first-line treatment of advanced NSCLC harboring EGFR mutations, the authors concluded osimertinib efficacy was superior when compared to gefitinib/erlotinib. A subsequent publication reported the median overall survival as 38.6 months (95%CI, 34.5 to 41.8) in the osimertinib group and 31.8 months (95%CI, 26.6 to

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Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: As regards safety, in the FLAURA trial overall, 98% of the patients in the two trial groups had at least one adverse event. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those randomized to gefitinib/erlotinib. Serious adverse events were reported in 27% of the patients in each trial group. A decrease in the ejection fraction was reported in 13 patients (5%) in the osimertinib group and in 5 (2%) in the gefitinib/erlotinib group, with no associated symptoms reported. QT prolongation on electrocardiography was reported in 28 patients (10%) in the osimertinib group and in 12 patients (4%) in the gefitinib/erlotinib group. There were no new reports of interstitial lung disease, which was reported in 6 patients (2%) in the osimertinib group and in 4 (1%) in the gefitinib/erlotinib group, or of pneumonitis, which was reported in 5 (2%) and 2 (1%), respectively. Fatal adverse events were reported in 9 patients (3%) in the osimertinib group and in 10 (4%) in the gefitinib/erlotinib group. None of the deaths in the osimertinib group and 2 in the gefitinib/erlotinib group were deemed by investigators to be treatment-related. In the osimertinib group, dose interruptions occurred in 120 patients (43%), dose reductions in 14 (5%), and permanent discontinuation of treatment because of adverse events in 41 (15%); in the gefitinib/erlotinib group, the corresponding numbers were similar - 113 (41%), 10 (4%), and 50 (18%).
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The benefit to risk ratio relative to no intervention or relative to conventional chemotherapy is beneficial. But the question is the benefit to risk ratio relative to EGFR TKIs already available including gefitinib, erlotinib and afatinib. The FLAURA trial a double-blind, phase 3 trial, randomly assigned 556 patients with previously untreated, advanced non–small-cell lung cancer (NSCLC) harboring *EGFR* exon 19 deletions or EGFR L858R mutations in a 1:1 ratio to receive either 80 osimertinib once daily) or physician's gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily. The primary end point was investigator-assessed progression-free survival. Although the objective response rate was similar with osimertinib (80%) and gefitinib/erlotinib (76%) (odds ratio, 1.27; 95% confidence interval [CI], 0.85 to 1.90; P=0.24), the median progression-free survival (PFS) was significantly longer with osimertinib than with gefitinib/erlotinib (18.9 vs. 10.2 months; hazard ratio (HR), 0.46; 95%CI, 0.37 to 0.57; P<0.001). A subsequent publication reported the median overall survival as 38.6 months (95%CI, 34.5 to 41.8) in the osimertinib group and 31.8 months (95%CI, 26.6 to 36.0) in the gefitinib/erlotinib group (HR 0.80; 95.05%CI, 0.64 to 1.00; P=0.046). This data favors osimertinib as regards benefit. The extent to which this outcome might be confounded by sequent therapies must remain speculative since their management was very dissimilar. At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the gefitinib/erlotinib group were continuing to receive a trial regimen; the median exposure was 20.7 months and 11.5 months, respectively. In total, 133 patients (48%) in the osimertinib group and 180 (65%) in the gefitinib/erlotinib group started a FIRST subsequent anticancer therapy after the discontinuation of the assigned treatment. That a lower fraction of those assigned to osimertinib received a subsequent therapy is expected given the longer duration of response with

	osimertinib. Of the 180 patients who received either gefitinib or erlotinib and then received a FIRST subsequent therapy, 85 (47%) received osimertinib as the FIRST subsequent therapy - 31% of the 277 who had received either gefitinib or erlotinib. Among the patients who received a FIRST subsequent therapy, the number of those who received a SECOND subsequent therapy was 72 of 133 (54%) in the osimertinib group and 92 of 180 (51%) in the gefitinib/erlotinib group. Thus, among all the patients who underwent randomization, the number of those who received a SECOND subsequent therapy was 72 of 279 (26%) in the osimertinib group and 92 of 277 (33%) in the gefitinib/erlotinib group. The lower percentages in those receiving osimertinib is also not unexpected given their longer duration of initial treatment would likely result in a smaller number progressing through the first salvage therapy at the time of analysis. However, given only 31% of those who received either gefitinib or erlotinib initially received osimertinib as a FIRST salvage therapy and no more than 25 received osimertinib as a SECOND salvage, only 40% could have received three EGFR TKIs. While one cannot reach definitive conclusions with the published data we do know that successive EGFR TKIs might slow growth and could provide a meaningful benefit.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Most of the evidence comes from the FLAURA trial, a randomized study that compared the efficacy of osimertinib to physician's choice gefitinib or erlotinib. The data is thus of very good quality. A comparison to another widely approved drug, afatinib, was not conducted. Also pending is information as to what might be the optimal sequence for administering the available EGFR TKIs.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: There are no special requirements that are not part of standard of care nor that would not be available where the proposed therapies would be administered.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: **https://www.who.int/publications/who-guidelines**)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost, and affordability of the medicine in different settings.	The submission acknowledges the problem of drug costs and is unable to provide a solution. They cite a study published in JAMA that evaluated the cost-effectiveness ratio for osimertinib in Brazil and the United States following the WHO cost-effectiveness threshold of three times the GDP per capita in each country. The primary endpoint was the Cost of Quality Years Gained (QALY) - ICER (Incremental Cost-Effectiveness Ratio). The study assessed the use of osimertinib as first line therapy in NSCLC harboring EGFR mutations and compared it to any of the 1st and 2nd generation EGFR TKIs frontline – note this is a comparison like that in the FLAURA clinical trial. A comprehensive model analyzed the drug acquisition' cost and the costs related to supportive care in adverse events and drugs prescribed after progression. Additionally, the authors conducted a sensitivity analysis to increase the results strength. The overall survival (95% CI) reported in the FLAURA trial (hazard ratio, 0.63; 95% CI, 0.45-0.88) had the strongest association with the ICER (ranging from $84 342 to $859 771). However, the authors conclude that at

	current costs and considering the willing to-pay thresholds, osimertinib is unlikely to be cost-effective as visit line therapy for NSCLC harboring EGFR mutations. In the United Kingdom, the National Institute for Health and Care Excellence (NICE), recently adopted osimertinib as standard of care in first line for locally advanced/metastatic NSCLC harboring EGFR mutations patients but only after a commercial agreement with the manufacturer to improve the cost-effectiveness ratio. The discount size is not public, and the consensus is that it is still much above what most countries could afford. A second less often discussed problem is the fact that the availability of therapies such as EGFR TKIs is of value only if all or most eligible patients are tested to find the few that might derive benefit from their use. This of necessity requires an investment in testing that in many countries is not possible.
Any additional comments	In the FALURA trial, in the osimertinib group, dose interruptions occurred in 120 patients (43%), dose reductions in 14 (5%), and permanent discontinuation of treatment because of adverse events in 41 (15%); in the gefitinib/erlotinib group, the corresponding numbers were similar - 113 (41%), 10 (4%), and 50 (18%). These numbers underscore the fact that despite its reported tolerability one in five needed dose reductions or discontinuation of therapy and nearly one half had dose interruptions. These percentages can be expected to be higher in the real world. Additionally, osimertinib like most oral agents, will suffer from the limited dosing options. Available in only 80 mg and 40 mg sizes, any dose reduction, will of necessity be a 50% reduction and few medicines are effective at 50% of the recommended dose – note there is not data for a two of three or three of four dosing schedule. Finally given the 20% reduction or discontinuation rates and an even higher rate in the real world, despite the importance of patient convenience, only a limited supply, possibly as little as a one-week supply, should be provided in the first few months until tolerability is well established, so as to avoid “wasting drug and resources”.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Osimertinib is an effective third generation EGFR TKI that is comparably tolerable to the 1st and 2nd generation TKIs that were developed before osimertinib. The FLAURA trial has confirmed its efficacy at a threshold that is tempting but many questions regarding the preferred sequencing of the various EGFR TKIs remain unanswered. Several 1st and 2nd generation EGFR TKIs whose patent protection has expired are available throughout the world at prices that are more affordable. Under these circumstances the cost of osimertinib cannot be ignored at this time but the drug deserves future consideration.
References (if required)	