A.30	Osimertinib – non-small cell lung cancer – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Osimertinib is a 3rd generation Tyrosine Kinase Receptor Inhibitor (TKI), directed towards the ATP binding site for the Epidermal Growth Factor Receptor (EGFR), which harbors mutations. The indication is 1st line treatment of EGFR mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The application states that this indication is definite, with no ongoing controversies, establishing an important role in lung cancer treatment with compelling public health interest. Despite novel treatments and several ongoing trials, advanced-stage EGFR-mutant NSCLCs remain incurable, and resistance to new TKIs still unresolved. As the application states, "(…) osimertinib is now considered the standard of treatment due to the efficacy and toxicity profile when no feasibility, cost, or affordability constraints limit the access." This is a possible impediment for adoption in most countries, irrespective of presence in the WHO-EML. The drug is very expensive and basically out of reach in countries that have not adopted it into a public provision system. There are two pharmaceutical forms available, as 80mg or 40mg film-coated tablet, as mesylate. The patent will only expire in 2035. There is one generic available, in Bangladesh. Osimertinib target population does not differ from the existing EGFR-TKI inhibitors, erlotinib and gefitinib, in terms of targetable EGFR mutation profile. Erlotinib and alternatives, afatinib and gefitinib, are already listed under 8.2.2 Targeted therapies in Complementary List. Due to the judgement of superiority (absolute) in respect to osimertinib. It is not clear to me if the present application is directed at adding (maintaining all 1st, 2nd and 3rd generation) to or substituting one of the above-mentioned substances (possibly erlotinib as first-line) in the Complementary list. Given the evidence, possibly eliminate the worst choice (less effective, more toxic). This recommendation is based upon to existing evidence of effectiveness and safety, and superiority over 1st and 2nd generation TKI options in the EML. However, if it is to be included as an EM careful consideration must be made towards availability and affordability by health systems, as an EM must, by definition, be always available, and this, frankly, will not, for a long time yet, due to cost and patent dynamics.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Lung cancer is the most incident type of cancer (2.12 million new cases in 2020), first among men (1.35 million new cases) and third among women (770 thousand new cases). It´s the most lethal among men and second among women. Incidence has decreased among men since the 1980s and women since the 2000s, due to smoking cessation[1,2]. Lung cancer has huge economic impact. Lost productivity in the BRICS countries is estimated at around $8 billion. Diagnosis occurs in advanced stages (III or IV, TNM 8). 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, for which the 5-yr survival rate is 18% (15% for men 21% for women). Only 16% of cases are i*n situ*, with a 5-yr 56% survival rate[2]. As osimertinib is directed towards the Epidermal Growth Factor Receptor (EGFR), it is important to point out that EGFR prevalence varies according to world region, risk factors and population phenotype. Prevalence stands at 47% (for the Asian-Pacific region) 36% (South America), 22% (North America), 21% (Africa), 15% (Europe), and 12% (Oceania).

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: For adults: the recommended regimen is 80 mg daily (1 tablet) until disease progression or unacceptable toxicity. Medical Oncology Society guidelines (i.e., ESMO, NCCN), regulatory, and HTA agencies endorse this. The application gives a grade 4 (high score) ESMO Magnitude of Clinical Benefit (ESMO-MCBS) in the **non-curative setting,** due to progression-free survival benefit (PFS gain) of 8.7 months ((HR) 0.46 (0.37-057), overall survival (OS) gain of 6.8). Osertiinib is recommended only for untreated locally advanced, metastatic NSCLC with EGFR sensitizing éxon 19 and L858R mutations detected by validated molecular tests according to regulatory agencies. EGFR TKIs **(1st, 2nd and 3rd generation) are the standard of care** for first-line treatment of metastatic NSCLC whose tumours harbor EGFR éxon18-21 sensitizing mutations. Osimertinib is adopted for a molecularly defined NSCLC population and produces a meaningful clinical benefit (Overall Survival gain of 6.8 months) linked to better toxicity profile. Improvement in cancer treatment is result of the magnitude of the target population. NSCLC represents the leading cause of death diagnosed as metastatic cancer, frequently where the EGFR mutation is the most frequent oncogene driver mutation (30% of cases). A SR &MA including 8 RCTs, 17.621 patients found no statistically significant overall survival difference in the first-line setting among 1st generation (gefitinib, erlotinib), and 2nd generation (afatinib) EGFR TKI. Another study compared the 3rd generation EGFR-TKI, osimertinib, with gefitinib and erlotinib for EGFR mutated NSCLC in metastatic patients until disease progression, unacceptable toxicity or consent withdrawal. In terms of efficacy, the primary endpoint, PFS favoured the osimertinib arm, (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57, P<0.0001) and also revealed meaningful clinical benefit for median Overall Survival in favor of osimertinib (mOs 38.6 months (95% CI 34.5–41.8) *vs* 31.8 months (95% CI 26.6–36.0) in the 1st generation TKI arm (HR 0.80, 95% CI 0.64–1.00, P=0.046). Osimertinib also revealed a statistically and clinically meaningful PFS benefit for patients with Central Nervous System (CNS) metastasis, a common site of progression and a frequent cause of Quality of Life (QOL) deterioration (mPFS 15.2 versus 9.6 months, HR 0.47, 95% CI 0.30–0.74, P=0.0009). In adjuvant therapy, a study including 9 RCTs and 3098 patients showed that osimertinib presented PFS benefit (HR 0.46, 95% CI 0.29–0.72) but not OS benefit (HR 0.87, 95% CI 0.69–1.11)[3]. Osimertinib has also shown better blood-brain barrier permeability, which impacts on CNS outcomes[4,5]. A SR&NMA including 57 trials - 36 studies and 24 interventions met the inclusion criteria for the NMA - compared osimertinib with erlotinibe-gefitinib and found benefits for PFS (HR 0.46 95% CI 0.33–0.64), but not so for OS (HR 0.8 95% CI 0.49–1.31)[6]. Despite improved initial response rates, patients treated with 1st or 2nd generation EGFR-TKIs may exhibit progression after 10–14 months, because of resistance. The application of irreversible EGFR inhibitors, such as afatinib is thought to overcome resistance, but toxicity limits use[7]. Osimertinib can form an irreversible covalent bond via the cysteine797 residue and T790M or other EGFR mutations, but also displays a resistance profile, result of mutation, amplification, gene fusion and other molecular mechanisms. Various clinical trials are under way to better comprehend and propose strategies (i.e.,fourth-generation TKIs, including combination therapies, antibody–drug conjugates, bispecific antibodies and immune-directed approaches) to counter this[8,9]. For children or adolescents under 18 there are no studies on effectiveness or safety.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: In a comparison between osimertinib and erlotinib/gefitinib, adverse effects profile was similar (FLAURA trial). Increases for stomatitis, fatigue and prolonged QT interval were seen for osimertinib. However, grade 3 or higher adverse event rates were 34% in the osimertinib group and 45% in the comparator group, making the overall toxicity profile better for the osimertinib group. Osimertinib is considered well tolerated. For children or adolescents under 18 there are no studies on effectiveness or safety.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: A MA studied safety of Osimertinib. The highest-incidence AE among AEs of all grades was diarrhea. Combined rate from 6 studies (579/1,303) was 44% (95% CI 36–52%). The second was rash, and the pooled rate of six studies (556/1,303) was 42% (95% CI 33–51%). Aggregated analysis of two studies on AEs of grade ≥III indicated that the highest incidence was a prolonged QT interval on ECG (10/489), and the combined rate was 2% (95% CI 1–3%). The second highest was neutropenia (9/489), and the combined rate was 2% (95% CI 1–3%). The pooled rate for five studies (12/1,132) with grade ≥III, was 1% (95% CI 0–1%)[7]. Tolerance / resistance, causes by molecular mechanisms is the main AE or efficacy failure, leading to disease relapse, and DFP must be monitored..
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: For detecting EFGR protein expression mutational analysis is the preferred method to assess the EGFR gene mutational status, and not immunohistochemistry. Molecular testing is is also a requirement for osimertinib treatment (Third WHO Model List of Essential in Vitro Diagnostics, 2021), (ICD11 code: 2A20.0Z) and the Medical Oncology Societies treatment guidelines. The indication follows the highest ESMO Scale for Clinically Actionability (ESCAT) Tier, reinforcing that the molecular test result supports the medicine's prescription according to the ESCAT best level of evidence. Prescription and use are thus dependent upon advanced diagnostics procedures, with external validation/quality assurance and sophisticated methodology carried out in specific testing platforms. Molecular diagnosis requires the same high-skilled workforce, and capacity building as proposed for gefitinib and erlotinib. For adults: the recommended regimen is 80 mg daily (1 tablet) until disease progression or unacceptable toxicity. Osimertinib can be taken with or without food, and omeprazole does not seem to impact on osimertinib pharmacokinetics. For children or adolescents under 18 there are no studies on effectiveness or safety.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Medicine is on-patent, which will only expire in 2035, if no patent extension is granted. A recent generic version is available in Bangladesh. The drug is very expensive and without public reimbursement or co-payment, most patients will not be able to afford treatment. In some countries it can be 10x the price of gefitinib and 3x the price of erlotinib (per tablet). Cost-effectiveness studies have been few. Even if they have been done, as the example given for Brazil and for the USA, the drug has not been considered cost-effective in Brazil and has not been examined by the National HTA Committee (CONITEC). The cited study concluded that "(…) osimertinib is unlikely to be cost-effective for EGFR-mutated first-line therapy". Osimertinib remains not cost-effective when compared to other TKIs, regardless of distinct thresholds, designs or settings.
Are there 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: There are two pharmaceutical forms available, as 80mg or 40mg film-coated tablet, as mesylate. Generics availability: Patent will expire by 2035, however a recent generic version is available in Bangladesh. The drug has been registers in several countries.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No WHO guidelines are available.

Additional References

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