A.11 Elexacaftor + tezacaftor + ivacaftor – EML and EMLc

Reviewer summary	☒ Supportive of the proposal (assuming price would be reduced, close monitoring for side effect is possible) ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): **Medicine:** CFTR modulators (fixed dose combination elexacaftor/tezacaftor/ivacaftor (ETI)); treatment is life-long, with daily oral medication; eligibility for CFTRm is genotype-dependent (88% of patients); the application reports that the combination is "predicted to increase life expectancy dramatically and improve overall quality of life" and if CFTR modulators are started in early childhood, median survival is likely to reach population norms. **Efficacy:** The results seem to suggest efficacy; however, that judgment is clouded by a number of issues listed below: • SR does not seem to be published or peer reviewed. • All included studies done in HIC; populations of diverse ages and gender. • The application provides ratings of the certainty of evidence but does not transparently provide the detailed judgments. • There are concerns with some of these ratings being moderate and high, which suggests that several factors might not have been considered: study design (observational); indirectness (reliance on surrogate outcomes; studies conducted in HIC); imprecision (some reported CI (e.g., for FEV1) cross the MID threshold, with a relatively low number of participants); inconsistency (not clear whether it was assessed and whether inconsistency was identified). • No MID identified for sweat chloride concentration, so the clinical significance of results are hard to interpret. *Of note:* The minimal important difference (MID) for FEV1 is in the range of 100 to 140 mL (American Thoracic Society/European Respiratory Society task force); regulators consider a change of 5 to 10% from baseline as clinically important. Studies show that FEV1 changes with elexacaftor, tezacaftor, and ivacaftor in patients with cystic fibrosis can reach the MID for FEV1. However, some individuals may not experience the full extent of improvement. Lung function potentially correlates with outcomes that are relevant to patients such as shortness of breath, reduced pulmonary exacerbations and exercise tolerance. Another benefit is the decreases in need for antibiotics associated with decrease in infection frequency. Over long periods this could lead to improving the natural history of the disease, reducing hospitalizations, intensive care admissions, the need for lung transplants, etc. **Safety:** Some of the adverse events are likely to be reversible and inconsequential on the long term (e.g., cough, rhinorrhea, headache). Other AEs are more concerning (e.g., anxiety, sleep disturbances, depression and 'brain fog'), but likely reversible with cessation or dose reduction. Adequate monitoring and assessment would be key. Here also there are concerns about the certainty of evidence (rated moderate or high) which is likely an overrating; unfortunately, the application does not transparently provide the detailed judgments. Moreover, the results are presented as relative effects and not as absolute effects, which is not optimal for making the judgement of safety. **Balance:** Probably favorable given the efficacy relates to preventing irreversible deterioration in respiratory function; AEs are mostly reversible but some (the neuropsychiatric AEs) are serious

	The absence of other cystic fibrosis-specific therapies on the list makes this combination a first in class, being the only therapeutic options for these patients at this time. **Special requirements for use:** need for close monitoring for neuropsychiatric AEs, so listing in the Complementary list is probably appropriate. **Budget issues:** "CFTRm are currently under patent worldwide with re-imbursement agreements reaching high prices in high income countries. Although lower prices are paid in some LMICs, they still grossly exceed the predicted cost of production which is estimated at US$5676 per person-year. Prices could be lowered if generic formulations entered the market as can be expected when the patent on IVA expires in 2025-2027". High quality evidence for dose reduction is lacking **Regulatory approval:** "CFTRm are approved by the US Food and Drug Administration, the European Medicines Agency and other high-income countries from age 2 years for ETI, and 1 month for IVA. Regulatory approval varies between agencies and countries according to age and CFTR variants" Does not seem available in most LIC. I expect, however, that families of patients with cystic fibrosis will be strongly motivated to have access to this medicine and that the medicine can be transferred from one country to another depending on availability of bioequivalent generics. This might pose an equity issue as not all families can travel. It should be seen as an interim solution before the medicine reaches a fair price.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable With concerns (see above)
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable With concerns (see above)
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
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 need for close monitoring for neuropsychiatric AEs
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☐ Yes ☒ No ☐ Not applicable

Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable