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

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): I support the inclusion of ivacaftor (IVA) as a monotherapy and the fixed dose combination elexacaftor/tezacaftor/ivacaftor (ETI) in the EML and EMLc. By repairing the damaged CFTR protein channel that pathogenic CF variations express, CFTR modulators stop the disease's progression and consequences. Adults and children receive daily oral medication at specified dosages as part of a lifelong course of treatment. ETI has radically transformed the profile of CF care by targeting the genetic basis of the disease when earlier medications gave symptomatic relief solely. Therefore, ETI stop the progression of the disease and influence a wider range of CF-related problems, such as pulmonary, nutritional, and chronic disease outcomes. ETI can also lower CF costs through reducing hospital admissions and slowing disease progression.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) At present, there are no alternative medications to CFTRm for the proposed indications on the Model Lists. Pancreatic enzymes, a supportive therapy with a role in alleviating some gastrointestinal features of CF, are listed on the complementary EML (EMLc) for children aged 1 month to 12 years. Currently no medications to treat the underlying cause of CF feature on the Model Lists.	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? 7 RCTs. Despite ETI being licensed in anyone over the age of two, most of the efficacy and tolerability evidence available (5/7 RCTs, 83%) was for pwCF ≥ 12 years. Only the RCT by Mall et al. and the RCT registered NCT05274269 included younger patient cohorts. Metanalysis 7 RCTs: **F508del mutations – Above 12 years old** Moderate-to-high certainty of evidence that ETI was more effective than both placebo and dual CFTRm therapy at improving ppFEV1 in pwCF over the age of 12 with cystic fibrosis (ETI versus placebo, mean difference (MD) = 14.24 [95% CI 12.79 to 15.68]; ETI versus TEZ/IVA, MD = 10.15 [95% CI 10.15 to 11.65]). Moderate-to-high certainty of evidence based on the GRADE criteria that ETI was more effective than both placebo and dual CFTRm therapy at lowering sweat chloride concentration in people over the age of 12 with cystic fibrosis (ETI versus placebo, MD = -41.43 [95% CI -43.86 to -38.99]; ETI versus TEZ/IVA, MD = -44.34 [95% CI -48.80 to -39.88]). **F508del mutations - Under 12 years old** Moderate certainty of evidence that ETI was more effective than placebo at both improving ppFEV1 (ETI versus placebo: MD = 11.00 [95% CI 1.81 to 20.19]) and lowering SwCl (ETI versus placebo: MD = -23.00 [95% CI -25.98 to -20.02]) in pwCF <12 years old. **Non-F508del mutations** Moderate certainty of evidence that ETI was more effective than placebo at both improving ppFEV1 (ETI versus placebo: MD = 9.30 [95% CI 7.31 to 11.29]) and lowering SwCl (ETI versus placebo: MD = -28.30 [95% CI-32.06 to -24.54]) in pwCF with non-F508del mutations.	☒ Yes ☐ No ☐ Not applicable

Does adequate evidence exist for the safety/harms associated with the proposed medicine? Metanalysis 7 RCTs: F508del mutations – Above 12 years old Moderate-to-high certainty of evidence that ETI was associated with similar AE and SAE rates compared to both placebo and dual CFTRm therapy in this population (ETI versus placebo, odds ratio (OR) AEs = 1.16 (95% CI 0.55 to 2.44), OR SAEs = 0.60 [95% CI 0.36, 1.01]; ETI versus TEZ/IVA, OR AEs = 1.20 (95% CI 0.70 to 2.05), OR SAEs = 0.66 [95% CI 0.30, 1.46]). F508del mutations - Under 12 years old Whilst ETI therapy was associated with a larger total number of total AEs than placebo in this population (ETI versus placebo: OR = 0.28 [95% CI 0.08 to 0.93]), the number of SAEs was comparable between ETI and placebo (ETI versus placebo: OR = 0.41 [95% CI 0.12 to 1.42]). Non-F508del mutations Moderate certainty evidence that ETI was associated with similar AE rates and SAE rates compared to placebo in this population (ETI versus placebo, OR AEs = 1.66 [95% CI 0.69 to 3.97]; OR SAEs = 0.59 [95% CI 0.28 to 1.22]).	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? There is evidence of notable and long-lasting improvements in important quantifiable CF outcomes, including sweat chloride, lung function, nutrition, and pulmonary exacerbations. It is anticipated that these advancements would significantly raise life expectancy and enhance general quality of life. It is predicted that median survival will approach population norms if CFTR modulators are initiated in early childhood. Few significant side effects have been documented, and CFTR modulators are often well tolerated.	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Eligibility for CFTRm is genotype-dependent and not all CFTR variants are responsive to therapy. Worldwide, over 2000 CFTR variants are identified to cause disease, and the majority respond to treatment, the most common being F508del. An estimated 88% of 111,767 people worldwide diagnosed with CF therefore stand to benefit from treatment.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Current list prices far exceed cost-effectiveness thresholds and estimations of cost of production. In the health technology assessments (HTAs) reviewed, prices ranged from US$100,000 to US$300,000 per-person-per-year, and an average of US$237,674. Under generic IVA production, anticipated with impending patent expiry, list prices fall by 46%, exemplified by the UK list price from US$237,720 to US$128,166. Alternate strategies to lower cost are the use of pharmacokinetic enhancement of CFTRm with strong CYP3A inhibitors such as ritonavir or clarithromycin which boost CFTRm levels, thus reducing the dose frequency while achieving similar clinical effect.	☒ 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? ETI, marketed as Kaftrio and Trikafta, is currently only approved in a limited number of countries. This is likely to be because the patient holder has not, thus far, sought approval in further countries. Currently, 99.88% of countries where ETI is not approved are low or middle-income. Similarly, 99.9% of countries where Kalydeco is not approved are low or middle-income countries.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable