A.29 Triple fixed-dose combinations of antihypertensives – EML

Reviewer summary	☒ Supportive of the proposal (with safeguards noted below) ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): **Medicine:** Fixed-dose combinations (FDCs) of antihypertensive medicines (including long-acting dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and thiazide or thiazide-like diuretics) **Efficacy:** It is worth noting the individual components of the FDC and their classes have been shown to improve morbidity and mortality outcomes. Also, reliance on surrogate measures (e.g., SBP, DBP) is likely a safe approach. Note: 2mm Hg is considered as the MID for both SBP and DBP as a reduction of 2 mmHg in resting SBP can decrease the risk of mortality from coronary heart disease, stroke, and all-causes by 4%, 6% and 3%, respectively (https://pubmed.ncbi.nlm.nih.gov/2807518/) Triple versus dual combination therapy: Meta-analysis suggests a reduction in SBP (by 5.4 mmHg) and DBP (3.2 mmHg) are likely to be clinically significant. (at 4 to 12 weeks) Larger percentage achieve blood pressure control (66.8% vs 50.2%); NNT=6 Fixed-dose combination therapy versus free equivalent combination therapy: Evidence supports significantly improved adherence, significantly improved persistence or lower discontinuation rates, significant reductions in SBP (by 3.99 mmHg) and DBP (by 1.54 mmHg) Low-dose combination therapy versus usual care Comparted to active comparators: significant reductions in SBP (by 7.4 mmHg) at 4 to 12 weeks; and by 6.4 mm Hg at 6-12 months. Also benefit in terms of the percentage achieving blood pressure control at 4 to 12 weeks **Safety:** Triple versus dual combination therapy: Low certainty evidence of increased risks of any adverse event (46.8% vs 36.4%), NNH= 10; and of treatment-related adverse events (20.7% vs 15.3%), NNH= 19; Very low certainty evidence of increased risk of withdrawal due to AEs (4.0% vs 3.0%); NNH=100. **Balance:** Slightly in favor when considering the extent of benefit and the extent of harm **Budget issues:** Cost of the FDCs compared to those of individual pills seems to vary across markets (from being lower, to similar to higher) FDCs likely to be cost-effective **Regulatory approval:** No major concern **Notes:** individual component medicines are listed on EML and present therapeutic alternatives Potential advantage of triple FDC is improved adherence and a reduced pill burden

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
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
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 Disclosure of higher rates of harms
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not applicable Need to note the potential higher prices depending on the setting
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