A.16	Fixed-dose combinations of cardiovascular medicines – prevention of atherosclerotic cardiovascular diseases – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Addresses a public health need, effective, safe and cost effective
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: • Cardiovascular diseases are responsible for one third of deaths globally (leading cause) and the burden continues to rise; largely driven by underlying atherosclerosis and ischemic heart disease • Current use of drugs to prevent and control atherosclerotic cardiovascular disease, including antiplatelet, cholesterol and blood pressure lowering drugs, remains exceedingly low over the past two decades despite high-quality evidence of their benefits as separate drug classes

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: • Large RCTs show that fixed dose combinations reduce the risk of cardiovascular disease events (nearly 50% relative risk reduction), including fatal and non-fatal myocardial infarction and stroke and need for revascularization in primary and secondary prevention settings. • Data analysed include trials where the comparator is usual care, placebo, or active drug therapy • **For high-risk primary prevention**, there is high-quality evidence that fixeddose combination therapy reduces the risk of fatal and nonfatal major adverse cardiovascular events by 29% (6.1% versus 8.4%, RR=0.71, 95% CI: 0.63, 0.79, I2=0%) • There is also high-quality evidence that fixed-dose combination therapy reduces the risk of all-cause mortality by 11% (5.6% versus 6.3%, RR=0.89, 95% CI: 0.78, 1.00, I2=0%) • These results are further corroborated with individual participant data metaanalysis conducted by the Polypill Trialists' Collaboration • A separate analysis of fixed-dose combination of blood pressure lowering + • statins + aspirin versus placebo indicates a nearly 50% relative risk reduction in cardiovascular disease events (HR = 0.53 [95% CI: 0.41, 0.67]) • Fixed dose combinations improve risk factor control and adherence. • **For secondary prevention**: 24% lower risk of the composite of cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization (9.5% versus 12.7%, HR=0.76, 95% CI, 0.60, 0.96) using the fixed-dose combinations of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) compared with high quality usual care.
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 primary prevention trials**: increase the risk of adverse events by 21% (11.6% versus 9.6%, RR = 1.21 95% CI: 1.12, 1.31, I2=15%, high-quality evidence); most adverse events were mild and reversible • **For secondary prevention trials**, there is moderate quality evidence that fixed-dose combinations increases the risk of adverse events by 7% (27.5% versus 25.9%, RR = 1.07 95% CI: 0.99, 1.15, I2=30%,

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: • The proposed fixed-dose combinations are contraindicated in women who are pregnant or breastfeeding
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: • baseline liver function and lipid levels are recommended • Serial lipid monitoring 6-12 weeks after initiation (and annually thereafter) is recommended for patients taking statins • WHO 2021 hypertension guideline recommend monitoring renal function and serum potassium "when starting or changing dose, if testing is readily available and does not delay treatment".
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: • Emerging Leaders survey: Most combinations found in this survey were affordable in the local context. • Fixed-dose combinations of statins and blood pressure lowering drugs with and without aspirin, including fixed-dose combinations proposed herein, are also highly cost effective
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:
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: • Guidelines are listed in Supplemental Appendix 1 • Also, medication classes included in these combinations are included in the Model List of Essential Medicines