Cardiovascular disease (CVD) remaining the leading global cause of death, accounting for 17.3 million deaths per year, a figure that is expected to grow to 23.6 million by 2030. The overall aging population projected to almost double by 2060 in Europe and the United States, the mere fact that majority of these patients in Low-Middle income countries are young and improving survival of patients who had ischaemic events ie coronary heart disease and cerebrovascular disease have created a large pool of patients eligible for secondary prevention. The administration of cardiovascular (CV) medications (e.g., statins, antihypertensive agents, anti-thrombotic agents) remains the most common medical intervention for secondary prevention of CVD.

Secondary prevention of cardiovascular disease has a potential to reduce the global morbidity and mortality worldwide of CVD pandemic burden. Clinical Trials data have shown each Blood Pressure (BP) lowering, statins, and antiplatelet drugs reduces mortality and recurrent heart attacks, strokes, after an acute ischemic event, and their combination is expected to reduce relative risk of events by 50 to 60%, however, fewer than 15% of patients receive these drugs in the long term.

Current information on their pharmacokinetics, impact on the risk factors, safety and tolerability has led to be recommended by WHO and adopted in the Europe, the US and Australasian guidelines to treat all people who have had a CVD event with blood pressure-lowering therapy, statins and aspirin, as well being offered lifestyle advice. Long-term use of these drugs, in a fixed dose combination or otherwise, is expected to reduce CVD risk by at least 50 – 60% in such groups

There are substantial treatment gaps in secondary prevention in countries at all economic levels, however, more compounded in Low-Middle Income countries where penetration therapy of all the three drugs is very low compared with high income countries.

Further, because of their lower incomes, these countries and their health care systems are less well equipped to deal with this burden than high income countries. CVD events and
deaths are more common among people who have already had a prior CVD event than those who have not had such an event.

Recent data highlight the massive treatment gap and room for improvement in secondary prevention on a global scale. Fixed Dose Combination therapy ie acetylsalicylic acid, atorvastatin and ramipril potentially provide bridging gap to implement an effective simple, and innovative solution to restrain the global CVD pandemic.

(2) Have all important studies/evidence of which you are aware been included in the application?

Yes ☒ No ☐

Please provide brief comments on any relevant studies that have not been included:

The application proposed inclusion of combination formulation Aspirin 100mg + Atorvastatin 20mg or 40mg and Ramipril 2.5, 5 or 10 mg as a fixed-dose combination Trinomia (Atorvastatin Version) as class of product and listing under the “square box” substitutable category as therapeutic alternatives limited to combinations with Aspirin 75-100mg + Atorvastatin 20mg or Simvastatin 40mg + or Ramipril 2.5mg or Enalapril 5mg or lisinopril 10mg or another dose-equivalent ACE inhibitor

Applicants provided relevant clinical studies on the evidence available on the efficacy, safety, tolerability, and affordability of FDC polypills for secondary prevention of CVD.

Major challenges inherited in developing formulations with bioequivalence and adequate stability (1), requires to be well tested on randomized clinical trials to elucidate their effects on clinical outcome - primary and secondary endpoints (2)

Recently published 6 March 2017 Cochrane Database Systematic Review demonstrated uncertainty of the effects of fixed-dose combination therapy on all-cause mortality or Atherosclerotic Cardiovascular (ASCVD) events. However, the event rates for these outcomes were very low, only five (all-cause mortality) and six (ASCVD) events out of 13 trials reported these outcomes, respectively, and these trials used usual care as their comparator. The uncertainty from this update suggests that future research will likely change this estimate. (2)

The trend toward greater number of ASCVD events in the group randomised to fixed-dose combination may be due to chance, performance bias due to lack blinding of the study personnel and participants, or the effects of switching or initiating the fixed-dose combination, but merits further investigation (2).
Adverse events were common in both the intervention (30%) and comparator (24%) groups, with participants randomised to fixed-dose combination therapy being 20% more likely to report an adverse event. Notably, no serious adverse events were reported. (2)

The trials reported reductions in systolic and diastolic blood pressure and total and LDL cholesterol. These risk factor changes would have been expected to result in a reduction in ASCVD events if sustained, but the trials reporting changes in risk factors were generally too short to detect a potential difference by their design. There was also substantial heterogeneity in these estimates, which might have been due to the characteristics of the participants studied, differences in the potency of the antihypertensives and statins used, and the differences in treatments used in the comparison groups, so these effects on risk factors should be interpreted with caution. (2)

The proposed listing of Aspirin 100mg + Atorvastatin 20mg or 40mg and Ramipril 2.5, 5 or 10 mg fixed dose combination as class product, not studied on randomized clinical trial neither meta-analysed on systematic reviews I am aware of; however, except a single economic model design study powered to assess the Cost-effectiveness on secondary cardiovascular disease prevention from improved adherence using a polypill, the design was reductionist model and simplified on the actual clinical decision-making and biological mechanisms of treatment and didn’t consider either individualisation of therapeutic dosing adjustments or treatment switching due to adverse events (3)

Nonetheless FOCUS trial 2014 (4) studied the fixed dose combination of Aspirin 75-100mg + Simvastatin 40mg + Ramipril 2.5mg the proposed formulation listing under the “square box” substitutable category as therapeutic alternatives, and demonstrated improved adherence and no statically treatment difference was found on systolic blood pressure and LDL cholesterol and adverse events, moreover, this fixed dose combination evaluated on recent published Cochrane Database Systematic Review (2) evaluating quality of evidence for fixed-dose combination therapy on adherence to be moderate due to indirectness of evidence based on the high quality care provided in the comparator - active drug comparator participants.

There is paucity of clinical evidence/randomized clinical trials/meta-analysis/systematic review on other proposed fixed dose combination to be listed on square box.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☒ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

Fixed dose combination containing aspirin, blood pressure (BP) lowering drugs, and a statin have demonstrated safety, substantial risk factor reductions, and improved medication adherence in secondary prevention of cardiovascular disease.
(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

Although the quality of evidence of fixed-dose combination therapy for all-cause mortality and ASCVD events considered to be low, due to indirectness of evidence, the comparator of usual care was of a higher standard than might be expected outside of the research setting and particularly higher than has been reported in low- and middle-income countries based on previous research, individuals who have low treatment rates at baseline are more likely to benefit, particularly relevant to patients in low and middle income countries where access and affordability to cost-effective secondary prevention is poor. Widespread use of a polypill will be vital as part of the strategy to reduce burden cardiovascular disease worldwide.

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☒

Please provide brief details:

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Fixed Dose Combination drug containing aspirin, blood pressure (BP) lowering drugs, and a statin have demonstrated safety, substantial risk factor reductions, and improved medication adherence in the secondary prevention of cardiovascular disease. Given their additive benefits, the combined estimated relative risk reduction (RRR) in CVD from both lifestyle modification and a combination pill is expected to be 70 – 80%.
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☒

Please provide brief details:

Fixed dose combination therapy is simplified strategy applicable for full scale implementation of secondary ASCVD prevention especially low-middle income countries, however, local models for implementation required to facilitate applicability in non-trial and less well-resourced settings. Such models have been developed and for are currently being trialled in PolyIran and HOPE-4.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

Please provide brief details:

Fixed dose combination drugs are registered by many national regulatory authorities and included on European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (ESC 2016), and the World Health Organization has identified fixed-dose combination therapy as a strategy to improve adherence (WHO 2016).

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☒ No ☐

Please provide brief details:

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies in 2016, identified fixed-dose combination therapy as a IIb, level of evidence B recommendation for improving adherence in the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (ESC 2016), and the World Health Organization has identified fixed-dose combination therapy as a strategy to improve adherence (WHO 2016).

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The fixed dose combination therapy improves adherence, substantial cardiovascular
risks reduction, readily acceptable to both patients and physicians across a range of settings and highly likely to be cost-effective and available for secondary prevention in people with cardiovascular disease in low and middle-income countries.

(10) Any additional comments? None

(11) Please frame the decisions and recommendations that the Expert Committee could make.

I recommend;

1. Fixed dose combination formulations of Aspirin 75-100mg + Simvastatin 40mg + Ramipril 2.5mg, 5.0mg, 10mg to be enlisted as class product

And

2. Fixed dose combination formulations of Aspirin 100mg + Atorvastatin 20mg or 40mg and Ramipril 2.5, 5 or 10 mg to be enlisted in “square box” substitutable category as therapeutic alternatives

Reasons

- The fixed dose combination of Aspirin 75-100mg + Simvastatin 40mg + Ramipril 2.5mg 5.0mg 10mg formulation has been studied on randomized clinical trial demonstrated improved adherence and no statically treatment difference was found on systolic blood pressure and LDL cholesterol and adverse events (4)

- This fixed dose combination formulation also evaluated on recent published Cochrane Database Systematic Review (2) evaluating quality of evidence for fixed-dose combination therapy on adherence to be moderate due to indirectness of evidence based on the high-quality care provided in the comparator - active drug comparator participants. (4)

- The fixed dose combination of Aspirin 100mg + Atorvastatin 20mg or 40mg and Ramipril 2.5, 5 or 10 mg lack evidence from randomized clinical trial, evidence available accrued from a single economic model design study powered to assess the cost-effectiveness on secondary cardiovascular disease prevention from improved adherence using a polypill, the design was reductionist model and simplified on the actual clinical decision-making and biological mechanisms of treatment and didn’t consider either individualisation of therapeutic dosing adjustments or treatment switching due to adverse events
**Implications for research**
High-quality randomised controlled trials are needed to evaluate if the effect of fixed-dose combination therapies on risk factor levels, translates into improvements in fatal and non-fatal events in secondary ASCVD-prevention settings. Ongoing trials will be informative and larger studies are also needed to evaluate the risk of serious adverse events in varied populations.

(12) **References** (if required)


