(1) Does the application adequately address the issue of the public health need for the medicine?  

<table>
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<th>Yes</th>
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The rationale for combination therapy is explained well by indicating that majority (50-70%) of the patients’ requires more than one drug for optimal management of hypertension. However, the clinical rationale is not confined to this specific FDC (Lisinopril+HCTZ) as stated in the application- “much the same clinical benefits can be expected from other ACEI-diuretic combinations (and indeed from other dual BP lowering combinations). “ The application states that this specific FDC is widely available and comparatively more affordable and thus should be considered. Individually, the two drugs are already part of EML.

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

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

The application provides the evidence for lowering of BP with this FDC when compared to monotherapy. Although, the effect on other cardiovascular outcomes for this FDC in comparison to monotherapy are not available, there is strong evidence indicating that combination therapy in general have better cardiovascular outcomes when compared to monotherapy¹.

Although, the combination of ACEI and a diuretic is one of the preferred combinations, the application does not discuss regarding benazepril–amlodipine (ACEI and calcium channel blocker) combination which was found to be superior to the benazepril–HCTZ combination in reducing cardiovascular events in the ACCOMPLISH trial².

The next issue is whether FDCs are better when compared to combination of two drugs separately. In a recent meta-analysis on existing RCTs indicated that he available low quality evidence does not confirm or rule out a significant difference between using a FDC versus a free drug combination³. This study concluded that well designed RCTs with a long duration of follow-up and assessment of morbidity and mortality outcomes are needed. Another previous meta-analysis of RCTs concluded that compared with free-drug combinations,
FDCs of antihypertensive agents are associated with a significant improvement in compliance and with non-significant beneficial trends in BP and adverse effects.

(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:

The application provides efficacy data (lowering of BP) for this FDC in comparison to placebo, monotherapy and other combinations. The efficacy in lowering BP is superior when compared to placebo and monotherapy. When compared to other combinations the efficacy is similar among the studies included in the application.

However, in the ACCOMPLISH trial the efficacy of ACEI+Diuretic combination in preventing adverse cardiovascular outcomes in high-risk patients was inferior to the ACEI+calcium channel blocker. For the primary outcome (composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization) there was an absolute risk reduction with benazepril–amlodipine therapy of 2.2% when compared to benazepril-hctz and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90; \( P<0.001 \)).

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

Yes, individually these two drugs been used in variety of settings (high income and low income countries) and thus were included in the previous EML. Similarly, this FDC is also used in diverse settings currently.

(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:

The FDC has higher events of dizziness, orthostatic hypotension when compared to placebo and when compared to lisinopril alone. Cough could be a concern from lisinopril in some patients.
(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Combination therapy has better cardiovascular outcomes when compared to monotherapy in treatment of hypertension. FDCs improve compliance, however there is currently no strong evidence to indicate that FDCs have better cardiovascular outcomes when compared to free drug combinations. Thus, the benefit to risk ratio is uncertain for this FDC. In addition, there is evidence to indicate that a different combination (ACEI + calcium channel blockers) has better efficacy data on cardiovascular outcomes when compared to the combination included in the application.
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:

(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:

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
   
   Yes ☐ No ☒
   
   Please provide brief details:

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

   The cost of this FDC is affordable with average price per pill being 0.75 USD. In India, the cost of FDC (lisinopril+HCTZ) is cheaper (4.2 INR per pill) compared to the cost of both drugs (4.7 INR for two pills combined) individually.

(10) Any additional comments?

   None

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

   Combination therapy has been shown to have better cardiovascular outcomes when compared to monotherapy in treatment of hypertension\(^1\). Given the recent strong evidence on benefits of lowering BP well below 140 mmHg, the need for combination therapy will increase\(^6\). FDCs are shown to improve adherence to prescribed drugs, however, current evidence does not confirm or rule out a significant difference in cardiovascular outcomes...
when using a FDC versus a free drug combination\textsuperscript{4,5}. In addition, there is evidence to indicate that another combination is superior (Benazepril+Amlo"cine) when compared to this particular FDC (lisinpril+HCTZ)\textsuperscript{2}. Considering these, I recommend that the committee should not consider including this combination in the EML at this time.

(12) References (if required)


