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

Yes ☐  No ☑

1. Public health importance of CVD is well known and evidence based.
2. Public health need for medical management of CVD is also well known and evidence based.
3. WHO as well as member countries are developing strategies to reach the “25X25” goal, that is to reduce the number of premature deaths (>30 and <70 years) due to NC chronic diseases (NCDs) by 25% by the year 2025.
4. One target to reach this goal is “At least 50% of eligible people receive drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes”
5. But the application has not addressed adequately how listing these FDCs in the model EML would achieve these targets.
6. Making “at least 50% of eligible people to receive drug therapy and counselling to prevent heart attacks and strokes” need other key interventions in LMIC before including a FDC into the EML. Examples include: Increasing availability in public health sector, improving the affordability, strengthening the health care services, minimizing manipulation by pharmaceutical industries, improving public awareness, strong national medicine policy, health insurance system, ensuring quality of medicines, etc (most of these are not evidence based as hardly any studies in these topics from LMICs are available in the literature)
7. Inclusion of FDC for communicable diseases (CDs) cannot be comparable with FDC for NCDs.
   a. FDCs in CDs has a great beneficial effects which is not seen in NCDs, that is to prevent emergence of drug resistance
   b. Potential for marketing is less with FDCs in CDs compared to FDCs for NCDs, so less pharmaceutical industry manipulation for FDCs in CDs
   c. FDCs in CDs have active components which work against the microbes, hence does not interfere with multiple physiological mechanisms in humans even more than one active ingredients are incorporated, but FDCs for NCDs will interfere with multiple and different physiological mechanisms in the body which can be difficult to manage compared to taking them as individual active ingredients
   d. Dose adjustment (or stopping) of an individual active ingredient would be a common occurrence with medicines uses for NCDs than CDs. FDCs are not ideal product for dose adjustments (or stopping) an individual active ingredient
8. Role of adherence to achieve at least 50% of eligible people to receive drug therapy and counselling to prevent heart attacks and strokes in LICs is different to that seen in HICs.
   a. Dynamics of factors influencing adherence differs between LICs and HICs
b. In some instances rate of adherence has been reported to be higher in resource limited settings compared to resource-rich countries supporting the above claim.

9. Evidence for improvement in adherence with FDCs compared to multiple tablets is not available from LICs.
   a. Taking more than one tablet has not been a major factor in influencing adherence in LICs.
   b. Providing FDCs as a strategy to improve adherence to drug therapy for chronic NCDs in real time practice is limited or not available from LICs. Publication are mainly from HICs.

10. Studies given in the application supporting that FDCs increases adherence have limitations (Table 5 in Section 10)
   a. Reference 13: 5 countries, 9 months follow up, Adherence measured by self-reported Morisky-Green questionnaire (MAQ) and pill count, adherence difference is 50.8% versus 41%, No treatment difference was found at follow-up in mean systolic blood pressure (129.6 mm Hg vs. 128.6 mm Hg), mean low-density lipoprotein cholesterol levels (89.9 mg/dl vs. 91.7 mg/dl), serious adverse events (23 vs. 21), or death (1, 0.3% in each group).
   b. Reference 14: Australia, 18 months, Adherence measured by self reporting, Adherence difference 70 vs 47%. No difference in SBP or cholesterol.
   c. Reference 15: New Zealand, 12 months, Adherence measured by self reported current use, Adherence difference 81 versus 46%. There was no statistically significant improvement in risk factor control between the fixed dose combination and usual care groups over 12 months.
   d. Reference 16: India and Europe, Mean follow up 15 months, Adherence measured by self-reported use of antiplatelet, statin, and 2 BP-lowering medications. Adherence difference 86% versus 65%. There were no significant differences in serious adverse events or cardiovascular events (50 [5%] in the FDC group and 35 [3.5%] in the usual care group; RR, 1.45; 95%CI, 0.94-2.24; P=.09) between the groups.

11. Adherence measurement: Measurement of adherence is very difficult. All the tools available have some limitations. Self reporting is not a reliable method, and self reporting during a controlled period (research period) will not predict what will happen in real settings.

12. Availability of FDCs could lead to “non-marketing” or “shortage” of individual components in LICs (no national medicinal policy, weak drug regulation, wide scale irrational prescribing/ dispensing, significant influence by pharmaceutical industry on prescribers, policy makers and pharmacists). We witnessed this with corticosteroid inhalers, with availability of combined (CS and long acting Beta 2 agonists), single CS is less marketed leading to shortage. This prompts even a rational prescriber to switch to combined inhalers.

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

   Yes [✓]  No [ ]

Please provide brief comments on any relevant studies that have not been included:
(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐  No ✓ ☐

See above (Response to question 1)

To include FDCs in Model lists they should have “a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately.”

The evidence is inadequate to support that there is proven advantage in compliance with this Aspirin FDCs over single compounds

Therapeutic effect: no advantage

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes ☐  No ✓ ☐

(5) 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 ✓ ☐

To predict safety of FDCs in NCDs which act on multiple mechanisms require large sample, uncontrolled study settings, and testing in diverse challenging settings. Not available

ADDITIONAL CONSIDERATIONS:

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

Yes ✓ ☐  No ☐

Dose adjustments, drug interactions with other medicines, measure to be taken when an adverse effect occurs for one component (example bleeding for aspirin, rhabdomyolysis for statin, etc) need specialized training to handle

(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 ☐

Limited countries

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

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

*Application provides estimation that it is cost effective. However, as I have pointed out, because of all other limitations, this cost effectiveness will not be handed down to countries/individuals especially in LMICs*

(10) Any additional comments?

*See above*

(11) Please summarise the action you propose the Expert Committee takes.

*Not to include*