19th Expert Committee on the Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for the inclusion of fixed dose combination therapy for secondary prevention of cardiovascular disease

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes   No ✓ (if no, please provide reference and information)

   The available efficacy data relates to the individual components, not to any of the FDCs that are proposed for listing. The only data for the FDC concept that was cited was in terms of self-reported adherence in a study which enrolled 2004 participants (ref 15). In this study, no difference in systolic blood pressure was shown between the group receiving the FDC and the group receiving usual care. The study was not primarily designed to measure hard outcomes, such as mortality.

   A meta-analysis of 6 studies (2144 participants) of “polypills” compared with placebo or component medicines in primary prophylaxis was published in 2012 (Elley CR et al. PLoS ONE 2012). The study duration varied from 6 weeks to 12 months. The study concluded that “Compared with placebo, the ‘polypills’ reduced blood pressure and lipids. Tolerability was lower amongst those on ‘polypills’ than those on placebo or one component, but differences were moderate.”

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   There is a claimed gain in adherence (a relative change of 33%) in comparison with usual care, when used for secondary prophylaxis or for primary prophylaxis in patients with a 5-year Framingham risk of 15% or more.

   In the primary prophylaxis meta-analysis it was reported that “Compared with placebo, the ‘polypills’ reduced systolic blood pressure by -9.2 mmHg, diastolic blood pressure by -5.0 mmHg, total cholesterol by -1.22 mmol/L and LDL cholesterol by -1.02 mmol/L.”

   c. Please provide any additional relevant information with reference

   doi:10.1371/journal.pone.0052145

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes   No ✓ (if no, please provide reference and information)
In the meta-analysis mentioned above (Elley CR et al. PLoS ONE 2012), discontinuation was used as a measure of tolerability. As reported: “Those taking ‘polypills’ were more likely to discontinue medication compared with placebo or one component (20% vs 14%) (OR: 1.5 (95%CI: 1.2, 1.9); Figure 4). There was lower heterogeneity (I² = 21%) than for the estimates of effects on blood pressure or lipids. When only comparisons with placebo were included, [32,33,34] the odds ratio was 1.7 (95%CI: 1.3, 2.3) (24% vs 16%). Amongst the four trials that reported overall side effects [31,32,33,36], the difference between ‘polypills’ and comparison arms in the proportion experiencing side effects (36% vs 28%) was not statistically significant (OR: 1.3 (95%CI: 0.7, 2.5; I² = 73%) (Figure 4). The difference approached significance when only placebo-controlled trials were compared (45% vs 33%) (OR: 1.7 (95%CI: 0.97, 2.9)).

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

No specific safety data on the polypill in secondary prophylaxis are as yet available, but the adverse effect profiles of the components are well-described.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability

a. Have all relevant data on cost and availability provided
   Yes ✔ No (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

While impressive projected costs/QALY have been provided, there are as yet no data on the price of quality-assured registered products.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

There appears to be some limited access in a handful of countries (registered in India, Guatemala, Mexico; applications mentioned in Argentina and Nicaragua). Review of two products (Polycap and Trinomia/Sincronium) by the FDA is referred to in the proposal, but no trace of such reviews could be found on the FDA website. A pragmatic approach to the registration of such FDCs has been called for, but the stance of major regulators is unknown (Sleight P, Pouleur H, Zannad F. Benefits, challenges, and registerability of the polypill. Eur Heart J. 2006 Jul;27(14):1651-6. Epub 2006 Apr 7).

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

That there is a need for access to effective and patient-appropriate secondary prophylaxis for cardiovascular diseases is not in doubt. Based on first principles, other conditions, and some early data on the FDCs, there is
expected to be an adherence gain from the use of combination therapy as opposed to multiple, single agents. Whether this will translate into clinical benefits or be associated with any untoward effects (e.g. additional adverse effects due to the inclusion of medicines that may not have been prescribed to a particular patient) is as yet unknown.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Mention is made in the proposal of proposed global NCD goals, and of the inclusion in those documents of targets for access to combined treatment. However, there is as yet no specific guideline which identifies exactly which FDC will be recommended for this indication.

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

This would require some access to information about patient selection, but no specialized training or equipment.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes ☑ No

7. Any other comments

The regulatory requirements for registering a multiple component FDC will include extensive bioequivalence studies. It is unclear whether the products used in clinical trials to date have been subjected to such evaluations (apart from the Polycap – ref v20). It is also noted that at least one prospective manufacturer (Dr Reddy’s) has abandoned development of an FDC product, citing the regulatory hurdles as one reason for this decision.

8. What is your recommendation to the committee (please provide the rationale)

Although there is wide acceptance of the CONCEPT of using a fixed-dose combination for the prevention of cardiovascular disease, this proposal has not presented a comprehensive review of the projected gains in either primary or secondary prophylaxis. The trial evidence provided is decidedly slim, with almost no indication yet of the potential safety concerns that may arise, especially in patients with established cardiovascular disease. The proposal also lists a range of options for inclusion:

a) Indian Polycap (low dose: aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg; high-dose: aspirin 200 mg, simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg)

b) Trinomia/Sincronium (aspirin 100 mg, simvastatin 40 mg, and ramipril (2.5 mg, 5 mg, or 10 mg))

c) Red Heart Pill 1 (aspirin 75mg, simvastatin (20 or 40mg), lisinopril 10mg, atenolol 50mg) and Red Heart Pill 2 (aspirin 75mg, simvastatin (20 or 40mg), lisinopril 10 mg, hydrochlorothiazide 12.5 mg)

None of these products is as yet registered by a stringent regulatory authority and their cost and availability are unknown. Some of the doses included seem questionable (e.g. the high-dose Indian Polycap with 200mg aspirin...
and an excessive dose of hydrochlorothiazide). The choices of the component active ingredients have also not been adequately addressed. There may be more affordable examples from each pharmacological class available or different choices supported by more extensive data (e.g. chlorthalidone instead of hydrochlorothiazide).

While the concept remain an attractive one, as evidenced by the large number of letters of support, the Committee needs to decide whether it is willing to make a largely symbolic gesture now, by including one or all of the proposed combinations, while knowing that global access will be slow and that sufficient evidence of efficacy, safety and cost-effectiveness are not as yet at hand. Accordingly, it is recommended that the application not be approved at this time, but that submission of an application supported by the necessary evidence is encouraged at a future date.