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

Yes [ ] No [X]

Please provide brief details:
HIV infection and AIDS-related illnesses affect most populations around the world. In sub-Saharan Africa and other resource-poor settings the disease pattern is mainly among heterosexual partners and vertical transfer from mother-to-child with a high disease transmission rate and burden. Owing to viral resistance and failure of effect with monotherapy, multiple drug therapy is recommended, just as is treatment compliance which potentially may be improved with a fixed-dose combination formulation.

The use of rilpivirine (US FDA pregnancy category B) instead of efavirenz (FDA pregnancy category D) as the NNRTI in a single-drug combination treatment with 2 NRTIs offers an opportunity for better patient compliance, while at the same time reducing the risk of viral resistance and providing a suitable treatment for adults more than 18 yrs of age which is also safer in pregnancy than efavirenz-based regimes.

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

Yes [X] 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 [X]

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:
This fixed-dose combination for HIV-1 infection, meets current WHO treatment guidelines by fulfilling the recommendation for two nucleoside/nucleotide analog reverse transcriptase inhibitor (NRTI) backbone (TDF + lamivudine (3TC) or Emtricitabine (FTC)) with a non-
nucleoside analog reverse transcriptase inhibitor (NNRTI) such as efavirenz (EFV), but with the replacement of EFV with a second-generation NNRTI, Rilpivirine (RPV).

Pooled data from the ECHO (backbone of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and THRIVE (backbone of zidovudine/lamivudine, or abacavir/lamivudine) trials, show that at week 48, rilpivirine 25 mg once daily and efavirenz 600 mg once daily, the third ARV added to the 2 others randomly in the respective trials, had comparable response rates regarding the primary endpoint of viral load of <50 copies per milliliter. Rilpivirine also showed improved tolerability versus efavirenz but had more virologic failures than efavirenz. [Cohen C] et al. J Acquir Immune Defic Syndr. 2012 May 1;60(1):33-42.]

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

Yes ☒ No ☐

Please provide brief details:
Emtricitabine + Rilpivirine + Tenofovir combination may have a role in treatment-naïve patients in settings with a high or increasing prevalence of primary resistance from first-generation NNRTI-associated mutations [Putcharoen et al, 2013]

In the setting of pregnancy, this combination, which avoids use of Efavirenz, which is replaced by Rilpivirine, provides similar efficacy without the potential safety-related issues

Black/African American and Asian patients together represented about 40% of the total patient population in both the ECHO and THRIVE studies

(5)  Has the application adequately considered the safety and adverse effects of the medicine?

Yes ☒ No ☐

Please provide brief details:
Applications for 2 components (FTC and TDF) of the combination have previously been reviewed.

The safety profile of the 3-drug combination in adult ARV-naïve HIV-1-infected subjects has been established from the ECHO and THRIVE trials. Which showed that RPV in the combination was associated with a lower incidence of treatment-related grade 2–4 adverse events compared with EFV in the combination.

Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☒
ADDITIONAL CONSIDERATIONS:

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

Yes [ ] No [x]

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 [x]

Please provide brief details:

RPV + FTC/TDF was first approved in 2011 in the United States for patients new to ART therapy. The European Commission granted a marketing authorisation valid throughout the European Union on 28 November 2011. In Dec. 2013 the U.S. Food and Drug Administration (FDA) approved it for treatment-experience individuals with no prior treatment failure or virus resistance to any of the components and who have viral loads <100,000 HIV-1 RNA copies/ml.

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

Yes [ ] No [x]

Please provide brief details:

The June 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend triple ARTs without RPV as follows TDF + 3TC (or FTC) + EFV or when this is contraindicated or not available, one of the following options is recommended: AZT + 3TC + EFV or AZT + 3TC + NVP or TDF + 3TC (or FTC) + NVP

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

A price tag for 30 tablets (one month adult treatment course) containing 25 mg RPV, 200 mg FTC, and 300 mg TDF of $2,185.36 (http://www.drugs.com/price-guide/complera accessed 6th April 2015) (Price range $2081.44 to $2252.76  http://www.goodrx.com/complera accessed 6th April 2015) will clearly not be affordable by the majority in developing countries without special government or non-governmental organizational support or other social mitigation or patient assistant scheme.

(10) Any additional comments?
(11) Please summarise the action you propose the Expert Committee takes.

Accept for inclusion with arrangements for cost reliefs and special pricing arrangements for low and middle income countries.