(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes X No

   Please provide brief details: Chronic hepatitis B has an enormous disease burden worldwide, and individuals are at risk for end-stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC, primary liver cancer). Treatment with potent nucleoside/nucleotide analogs such as Tenofovir (TDF) has been shown to significantly reduce the risk of liver disease progression and possible HCC development. TDF is well tolerated, highly potent, and unlike first generation oral anti-HBV drugs, no risk of observed antiviral resistance was observed even after years of therapy. Treatment leads to regression of fibrosis and reversal of cirrhosis. However many patients worldwide, especially in countries with the greatest burden of HBV infection, do not have access to effective anti-HBV therapy.

(2) Have all important studies that you are aware of been included in the application?
   Yes X No

   - Benefit based on data from 8 years of follow-up in two pivotal ongoing Phase 3 clinical trials, and confirmed in real-world studies.
   - Please provide brief comments on any relevant studies that have not been included:
     - Ongoing studies on TDF use in pregnancy (www.ClinicalTrials.gov Identifier: NCT01488526; NCT01745822)
     - Ongoing Phase 2 studies of TDF vs. new formulation Tenofovir Alfenamide

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes No

   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:
   - Treatment leads to regression of fibrosis and even cirrhosis – based on paired liver biopsies.
   - Effective in patients with documented HBV resistance to other antiviral agents.
   - Benefits demonstrated in achieving surrogate end-points included virological, biochemical and serological responses.

(4) Is there evidence of efficacy in diverse settings and/or populations?
   Yes X No
Please provide brief details:

- Adults, treatment naïve and experienced
- Both HBeAg positive and HBeAg negative CHB patients
- Decompensated liver disease
- Active viral replication with active histological inflammation and/or fibrosis
- No well controlled studies in pregnancy
- Insufficient information in the effects of tenofovir in newborn
- Not approved in pediatric patients (under age 12), and weigh <25 kg

(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 X No □

Please provide brief details:

- Limited studies in elderly (>age 65) and should be used with caution given the greater frequency of impaired hepatic, renal or cardiac function
- Assess at baseline and monitor CrCl on treatment
- Avoid co-administration with concurrently nephro-toxic drugs
- Requires renal dosing if GFR <50 ml/min, primarily excreted by the kidney
- Renal failure, renal impairment, hypophosphatemia, proximal tubulopathy has been reported in clinical practise
- Interrupt if CRCl, 50 L/min or serum phosphate <1.0 mg/dL
- Decline in bone density after treatment initiation that stabilized (plateau)
- Drug interactions with didanosine, HIV-1 protease inhibitors, and Adefovir Dipivoxil
- Overall treatment is well tolerated in both clinical and real-world studies
- Most common side effect reported was nausea in compensated liver disease; decompensated liver disease nausea, pruritis, dizziness
- Estimated post-marketing exposure 2,928,235

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:

- Expertise in the management of chronic hepatitis B infection
- The treatment does not eradicate the virus. Patients who develop virological breakthrough may be at risk for severe hepatitis B disease flares, and liver disease decompensation. Cessation of therapy in non-cirrhotic patients should be done carefully on a case-by case basis, and monitored closely. Treatment cessation is not recommended in cirrhotic patients who have limited hepatic reserve and may not tolerate severe liver disease flares.
(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:
- Off-label use in pregnancy
- Not recommended in nursing mothers although available data suggest risk is low (see notes below).
- Recommended as first line therapy for chronic hepatitis B by most major international guidelines (i.e., AASLD, EASL, APASL)

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

Yes ☐ No ☐

Please provide brief details:
Published in the first set of WHO management guidelines for patients with CHB, and recommended as both first-line therapy and as the preferred therapy for patients with documented resistance to other antiviral agents

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

Gilead has established licensing agreements with generic drug manufacturers in many low-medium income countries, granting rights to sell high-quality, low-cost generic versions

(10) Any additional comments?

The application states that as “a general rule HBV infected mothers should not breastfeed”. There is very limited data supporting the risk of HBV transmission in breast milk, especially in infants that receive the complete HBV passive/active immunoprophylaxis regimen. The application also does not recommend breastfeeding whilst taking TDF, as it is excreted in breastmilk. Available data, animal studies, as well as general expert consensus opinion (including the CDC) suggest the excretion in breastmilk is minimal, and drug exposure is lower through breastmilk than in utero. The overall benefits of breastfeeding outweigh the risk of HBV transmission (in vaccinated infants) or drug exposure, and in low-medium income countries is the safest and most nutritious for all infants.

(11) Please summarise the action you propose the Expert Committee takes.
Addition to the WHO EML