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

Yes ☒ 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 (primary liver cancer). Treatment with potent nucleoside/nucleotide analogs such as Entecavir (ETV) has been shown to significantly reduce the risk of liver disease progression and possible HCC development. ETV is well tolerated, highly potent, and unlike first generation oral anti-HBV drugs has a low risk of antiviral resistance in treatment naïve patients, even after years of therapy. 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 ☒ 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 ☐

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: Older oral anti-HBV drugs (i.e., lamivudine, telbivudine, adefovir) have a lower barrier to resistance and risk of treatment failure. These drugs are not recommended by most global expert guidelines. Treatment has been demonstrated to be effective in virological (i.e., viral load suppression), histological and biochemical markers of liver disease. ETV has been demonstrated to reduce and reverse HBV-related liver disease progression and risk of HCC. The risk of drug resistance in treatment naïve patients is minimal (i.e., <2%) with long-term therapy.

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

Yes ☒ No ☐
Please provide brief details:
- Both HBeAg positive and HBeAg negative
- The drug has also been used in children who need treatment (age 2-11).
- The drug is effective in patients with decompensated cirrhosis.
- Tenofovir has potential nephrotoxic and affects bone remodelling. Thus, entecavir is preferred over tenofovir in patients with renal disease (renal dosing) as well as those with severe metabolic bone disease.
- Resistance to other nucleos/tide analogs (i.e., lamivudine, adefovir) increases the risk of developing ETV resistance, thus the drug is recommended mainly for treatment naïve CHB patients.

(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: In patients with decompensated cirrhosis treatment with nucleoside/nucleotide analog (i.e., entecavir) has been associated with lactic acidosis, although no dosage adjustment is required. In addition, ETV has anti-HIV activity, thus in HBV/HIV coinfection ETV should only be used in patients in which HIV replication is well controlled. Dosage adjustment is recommended in patients with renal impairment. Otherwise the drug is very safe and well tolerated.

ADDITIONAL CONSIDERATIONS:

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

Yes X No

Please provide brief details: All patients should be monitored for treatment response and adherence to therapy, especially if cirrhotic. Patients who develop virological breakthrough on treatment due to drug resistance or non-compliance 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. There is limited safety data in pregnancy and should not be used.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes X 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: Entecavir is listed as first-line therapy for management of chronic hepatitis B in the recently published WHO guidelines (March 2015).

(9) **Please comment briefly on issues regarding cost and affordability of this medicine.** ETV and Tenofovir for hepatitis B, has the lowest risk of antiviral resistance with long-term treatment with the best safety profile. Entecavir is relatively inexpensive and also highly effective and should also be approved.

(10) **Any additional comments?**

-- The WHO recommends AFP and US for HCC surveillance, many expert guidelines do not recommend AFP due to low sensitivity/specificity. Thus US should be the only mode of surveillance.

Multiple foundations support inclusion of HBV, ETV is listed for use in over 60 countries, and many generic formulations are available, and studies of over 9000 patients published.

- Organizations that supported this application include:
  - World Hepatitis Alliance
  - Médecins sans Frontières
  - Coalition to end Viral Hepatitis in the Western Pacific (CEVHAP)
  - Asia and Pacific Alliance to Eliminate Viral Hepatitis (APAVH)
  - Hepatitis B Foundation
  - Bristol-Meyers Squibb Corporation

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

Approval on WHO list of essential medicines