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

   Please provide brief details:
   One third of the world population are infected with hepatitis B virus while 240,000,000 are living with chronic infection. Generally, 30% of cirrhosis and 53% of all hepatocellular carcinoma deaths are attributable to hepatitis B virus infection. Despite the above it is only tenofovir that is included in essential medicine list for treatment of hepatitis B virus.

(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:

   The following were not included

   1. Efficacy of entecavir treatment for up to 96 weeks in nucleoside-naive HBeAg-positive chronic hepatitis B patients with high viral load.
   Yan LB1, Chen EQ1, Bai L1, Du LY1, Chen LL1, Liao J1, He M1, Tang H2.

   CONCLUSION:

   The baseline HVL was a negative predictor of virological response in CHB patients with ETV monotherapy. For those HVL patients treated by ETV with poor VR, which defined as HBVDNA>1000copies/mL at week48, the treatment strategies need to be adjusted.

   2. Comparison of the antiviral effects of different nucleos(t)ide analogues in chinese patients with chronic hepatitis B: a head-to-head study.
   Yu S, Zhou Q, Zhao XM, Yuan M, Wang CT, Cheng XG, Zhang ZH1, Li X1.

   CONCLUSIONS:

   Different nucleos(t)ide (NUC) analogues tested exhibited no significant differences in effectiveness for Chinese NUC-naive HBV patients during 1-year treatment period.

   3. Entecavir has high efficacy and safety in white patients with chronic hepatitis B and comorbidities.
CONCLUSION:

Entecavir is safe, well tolerated, and highly effective, even in patients with comorbid condition(s). Discontinuation of treatment in patients who have not been cleared of HBsAg may lead to virological recurrence.


The alanine aminotransferase normalization rate, serological response, and adverse event rate were also not significantly different between entecavir and tenofovir at 24 or 48 weeks after treatment. These results suggest that tenofovir is a better choice to treat chronic HBV patients than entecavir as it is better able to suppress HBV viral load and has a similar safety profile.

(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:

Entecavir caused a high percentage of undetectable HBV DNA and normalized ALT compared to Adefovir
Greater improvement in liver histology and HBV DNA loss than those treated with Lamivudine

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

Yes ✔ No □

Please provide brief details:

Evidence exist among different populations e.g. Asian versus Non-Asian
Children: placebo controlled trial of entecavir in children (ongoing) but data reported to FDA new drug application process, entecavir was superior to placebo at reducing HBV DNA to <50 IU/mL and HBeAg seroconversion (24% versus 2%)
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 □

Please provide brief details:

*Use in Pregnancy: Only if the benefit outweighs the risk*

*Dose adjustment is recommended for patients with creatinine clearance <50 ml/min*

**ADDITIONAL CONSIDERATIONS:**

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

Yes □ No √

Please provide brief details:

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:

*FDA and EMA approved*

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

Yes √ No □

Please provide brief details:

*NICE guidelines*

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

*Entecavir is expensive and may not be affordable in a low resource setting. For those who can afford it, availability may be an issue as only one manufacturer is licenced in USA and non in Africa.*
(10) Any additional comments?

Nil

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

Entecavir should be included in Essential Medicines List.