NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)
Entecavir for the treatment of chronic hepatitis B

Appraisal consultation document

Comments submitted by [redacted] Royal College of Physicians

Response coordinated by [redacted]

[redacted]

i) Do you consider that all of the relevant evidence has been taken into account?

The most appropriate place for entecavir in the pathway of care of hepatitis B is to suppress HBV DNA replication in patients with ongoing evidence of HBV replication, raised serum ALT and evidence of advancing disease. Entecavir could be used more effectively than lamivudine for patients with raised serum aminotransferases (> 2x the ULN) and active levels of HBV DNA replication, (> 10^5 copies/ml) as viral suppression is more effective in this group, and resistance rates are far lower. This was demonstrable in both HBeAg positive and negative patients. It is important to reduce levels of replication in both HBeAg positive and negative patients with evidence of active HBV replication; lamivudine is currently used in combination in the UK for most patients with either high levels of replication (>10^6 copies/ml) or advanced disease.

Pegylated interferon is not widely used for first line treatment for HBeAg negative patients in the UK, although so recommended by NICE. This is largely related to patient choice, given the side effect profile of interferon, and the high relapse rates observed in this group. Pegylated interferon is often contraindicated in patients with cirrhosis and is problematical in patients with decompensated cirrhosis. Entecavir leads to rapid viral suppression low rates of resistance, and effective suppression of HBV DNA replication in both HBeAg positive and negative patients, and would be considered for treatment of both these groups of patients, with HBV DNA levels of > 10^5 copies /ml.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The ICER for treating HBeAg negative patients are noted; the differential ERV probability analysis of 4% for entecavir being cost effective at a willingness to pay of £20,000 and 40% at a willingness to pay of £30,000 when compensated cirrhosis is also considered is puzzling given the responsiveness of patients with cirrhosis, most of

whom have lower levels of HBV DNA and are HBeAg negative. The structural elements of the model including cirrhosis need re-examination.

It is difficult to provide categorical evidence using models that include assumptions that have several uncertainties. There are differences that pertain to clinical practice within existing NICE recommended treatments for hepatitis B. For example, there is increasing awareness of the association between persistently raised HBV DNA (> 10^4 copies/ml) and ALT in large cohorts of Chinese patients and the subsequent risk of cirrhosis and HCC. Whilst incomplete, these date indicate the risk of persistent HBV infection to infected individuals, which may change existing equations for modelling progression. I note the ERV groups' sensitivity analysis using different utility values. Caution should be interpreted in using transition probabilities in current Markov models; the majority of Asian patients who develop decompensated cirrhosis or HCC are HBeAg-negative, and treatment is indicated to suppress levels of replication in these patients at risk.

The majority view is that clinicians regard this drug as a valuable addition to our treatment options. The very low resistance rates will allow a reduction in the prevalence of resistant viral strains and will permit prolonged monotherapy.

We are however surprised to find that the calculations show the drug to be non-cost effective for HBeAg disease. Many clinicians are now using lamivudine + adefovir as first line therapy for the majority of patients with this condition. A stepped care approach (lamivudine followed by adefovir) is not utilised in many centres in the UK, because of the risk of engendering sequential lamivudine and adefovir resistance. Generally, lamivudine and adefovir are prescribed *de novo* for patients with high levels of resistance.

However recent data from Sung et al (Journal of Hepatology 2008) indicate that high rates of resistance can be observed in patients treated with this combination after two years of treatment (15%), and more appropriate combination therapy is being sought. Sequential monotherapy is a clinically dangerous strategy in patients with cirrhosis because of the risk of exacerbation. This will apply equally to HBeAg positive patients and HBeAg negative patients with high levels of HBV replication (> 10^5 copies/ml).

Since entecavir is cheaper than the current combinations the clinical community is surprised by the results of the analysis and it would be helpful to look into the cost effectiveness of entecavir compared to a large proportion of patients receiving combination therapy. In particular a review of the cost effectiveness calculations in patients with cirrhosis (the vast majority of whom receive combination therapy ab initio) would be helpful.

We note that further data on the cost effectiveness of entecavir in patients with cirrhosis has been requested and we hope that this will provide the evidence required to allow a positive opinion for patients with HBeAg negative disease.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

We note the ERV critique of the decision problem not to include patients with advanced liver disease. It is crucial that safety and efficacy data are obtained in this group, who require rapid and effective suppression of HBV replication. It is likely that requests to use this agent in patients with advanced liver disease "decompensated liver disease" will understandably be made, in order to rapidly reduce HBV replication and improve liver function, or to suppress viraemia prior to liver transplantation to prevent recurrence. The most appropriate place for entecavir in the pathway of care of hepatitis B is to suppress HBV DNA replication in patients with ongoing evidence of HBV replication, raised serum ALT and evidence of advancing or advanced disease. Entecavir could be used more effectively than lamivudine or lamivudine and entecavir in combination for patients with raised serum aminotransferases (> 2x the ULN) and active levels of HBV DNA replication, (> 10^5 copies/ml) as viral suppression is more effective in this group, and resistance rates are far lower.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

Importantly, entecavir is an effective treatment of hepatitis B with ongoing viral replication, and the economic data presented, which will potentially restrict the drug to patients with only HBeAg in serum, is not clinically meaningful in our current state of knowledge given that patients should be categorised by age, stage of disease, serum ALT, HBV DNA levels in addition to HBeAg status.