NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Telbivudine for the treatment of chronic hepatitis B

Appraisal consultation document

Comments submitted by [redacted], Royal College of Physicians

Response coordinated by [redacted]

Conflict of interest: [redacted].

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

The pivotal telbivudine study design improves upon previous evaluations of nucleosides, as the design included a 2 year assessment of efficacy and resistance, after continuous therapy- a situation that realistically approximates current continuous use of nucleoside analogues for most patients. A large number of both HBeAg positive and negative patients were included. These are strengths of the study design. Telbivudine clearly has greater potency than lamivudine in terms of DNA suppression. It is more difficult to discern differences in HBeAg seroconversion rates on treatment between these agents but the two year data indicate that 38% of patients with ALT between 2 and 5 times the ULN lost HBeAg, compared to 29% of lamivudine treated patients. These rates approximate those seen after one year with pegylated interferon.

Generally HBeAg loss or seroconversion has not been measurably greater with more potent agents at one year; It may be that an immune response is required to achieve and sustain HBeAg loss in a greater percent of HBeAg positive patients. It is also difficult to quantitate differences in histological outcome between comparator agents at one and two years, given the time required for necroinflammatory and fibrosis repair; however improvements from baseline are noted. It is correct that a subset of patients with raised serum ALT have been analysed in this study but the subset reasonably pertains to a clinically defined group for whom hepatitis treatment is indicated. As pointed out in an earlier submission, and recognised by the Evidence Review Group report, resistance does emerge at a slower rate than lamivudine; however, its rate is clinically significant in patients who do not show a rapid decline in viraemia. This is a disadvantage of telbivudine compared to other more recently tested agents, and will require close DNA monitoring for early salvage in patients who develop resistance. These data require that for patients with high viral loads, further data regarding de novo combination treatment is required.

ERV references: The missing references sited by the ERV were in fact posters and presentation abstracts of the Digestive Disease Week of 2007 not the 108 th AASLD meeting (AASLD has held 58 meetings)

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?

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 serum ALT in large cohorts of Chinese patients and the subsequent risk of cirrhosis and HCC. Whilst incomplete, these date indicate the risk to infected individuals of persistent HBV infection, which may change existing equations for modelling progression. There should be some caution in calibrating these models given the current level of uncertainty of assessing the natural history of hepatitis B in the UK population.

The approach used for modelling HBeAg negative and positive disease appears reasonable given the different natural history of these diseases. The time horizons are reasonable. It is noted that 63% of HBeAg positive patient and 57% of HBeAg negative patients in globe study had ALT > 2 ULN; Although this group were not predefined, their inclusion in an analysis mirrors clinical practice and indications for treatment in several guidelines. In the HTA model, resource use estimates that patients were seen 11 times annually; in fact patients given nucleoside analogues are seen at 3-4 monthly intervals i.e. three times per year. We note that for HBeAg positive patients (page 79) telbivudine has a 71% and 49% probability of being cost effective at a willingness to pay threshold of £20,000 for HBeAg positive and negative patients respectively. We also note the data from table 4 (page 81) which I take to imply that neither lamivudine followed by adefovir nor lamivudine has a greater than 50% probability of being cost effective at a threshold willingness to pay of £20,000 per QALY?

The ITT analysis should indeed be presented as a modified ITT analysis - 6 patients were randomised and did not receive study drug; however these numbers would not materially affect the results. 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. Adefovir will rapidly lose importance in treatment, relative to tenofovir, given its lack

of potency in HBeAg positive patients, the poor primary response observed in 30%, resistance rates after 2 years, as well the relative cost of these agents.

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?

The most appropriate place for telbivudine in the pathway of care of hepatitis B remains to be determined, but based on the available evidence, telbivudine could be used more effectively than lamivudine for patients with raised serum aminotransferases (> 2x the ULN) and lower levels of hepatitis B replication, as viral suppression was more effective in this group, and resistance rates were lower. It remains to be determined whether telbivudine would be used as a monotherapy or in combination, but it seems clear that for patients with higher levels of replication (> 10^6 copies/ml) combination therapy, as for lamivudine will become the norm. Lamivudine is effectively 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 positive patients in the UK, and less so for HBeAg negative patients, although so recommended in NICE. This is largely related to patient choice, given the side effect profile of interferon. Pegylated interferon must of course be a consideration for appropriate patients. Telbivudine and entecavir clearly have different resistance profiles, but the indirect visual comparison with entecavir for cost effective analysis is problematic given the differing study designs and measurements. The study design of the entecavir HBeAg positive and negative trials leaves much to be desired and have been repeatedly criticised.

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

NICE approval of telbivudine should lead to clinical guidelines based on evidence that will direct the appropriate use of telbivudine, avoiding resistance. Of relevance, the current NICE guidelines must be questioned, given the current evidence that lamivudine is not considered an optimal first line monotherapy drug for the treatment of hepatitis B. Telbivudine may be suitable for patients with lower levels of HBV replication and where close monitoring for resistance is in place.