British Infection Society: Response to the Appraisal Consultation Document on Entecavir

## The British Infection Society

The British Infection Society is a charitable organisation representing 950 professionals (the majority being infectious disease physicians and microbiologists) working in the field of infection. Many of our members are directly involved in the management of and research into chronic hepatitis B infection. The comments below reflect a consensus view from those members with particular expertise and experience in the area of hepatitis B.

## General comments on the STA

This STA examines the utility and cost effectiveness of entecavir for the monotherapy of chronic hepatitis B infection. It is the view of the BIS that such appraisals, while helpful in some respects, are of limited value. We believe that there should be a more general appraisal of the management of chronic hepatitis B infection, taking into account not only the individual drugs available, but also considering treatment strategies (interferon versus antiviral drugs, combination therapy versus monotherapy), and the cost effectiveness of patient stratification using genotyping. We recognise that this would be a difficult undertaking. The decisions involved would be complex, and there is a lack of data to support some analyses. However we would encourage NICE to consider a wide ranging assessment of the overall management of chronic hepatitis B infection as its next step.

## Comments on the ACD

i) We are not aware of any important evidence relating directly to entecavir that has been excluded from the appraisal. However we do believe that the wrong emphasis has been put on the comparison between treatment with entecavir and with interferon. These two drugs represent different treatment strategies, and it is difficult to compare them directly. Many experts believe that interferon should be the treatment of choice as initial therapy (in the absence of decompensation), especially in HBeAg positive patients with genotype A virus, with a switch to antiviral therapy in interferon non-responders. The reasons for this are:

- Interferon is given for a defined period of time, as opposed to antivirals, which have no defined treatment period, and may need to be given for life.
- Interferon is more likely than currently available antivirals to induce sustained immunological control of the virus following a short (24 or 48 week) course. (In genotype A HBV up to 47% of patients may lose their expression of HBeAg , with 96% of those who do so remaining eAg negative after 3 years.)
- Unlike antiviral therapy, failure to respond to interferon treatment does not compromise in any way subsequent treatment with nucleoside analogues.

We also believe that new evidence on other antiviral agents should be taken into consideration in the appraisal. Since the ACD was compiled, significant new data on tenofovir have been published, and the drug has been licensed by the EMEA for the treatment of chronic hepatitis B infection. While this is not the place for a detailed exposition of the utility and cost effectiveness of tenofovir these data should at least be discussed.

ii) There is no doubt from the available evidence that entecavir given as monotherapy produces a more rapid virological response than either lamivudine or adefovir. There are no data as far as we are aware assessing directly the rapidity of viral response to entecavir compared to combination therapy with the two drugs given together. Speed of viral control is important for the successful long term complete suppression of viral replication, and may be a factor in decreasing the emergence of viral resistance.

It is also clear that the likelihood of virus developing resistance to entecavir is much lower than it is to either lamivudine or adefovir (when any of the 3 drugs are given as monotherapy). This has been observed in a clinical trial setting, and is also supported by theoretical evidence. Entecavir requires 3 separate gene mutations to become resistant to entecavir, a circumstance which is unlikely to arise due to spontaneous mutation in the absence of selection pressures. However there is evidence that pretreatment with lamivudine and adefovir will decrease the genetic barrier to resistance to entecavir, and that resistance to entecavir will become more prevalent. This may be of major importance in patients treated for long periods of time (we believe that the estimate of 2 year treatment duration is overly optimistic, even for HBeAg positive virus, and that treatment durations will be for many years, and possibly life).

The efficacy and resistance data suggest that entecavir monotherapy is a better first line treatment for chronic HBeAg positive chronic hepatitis B infection than either adefovir or lamivudine monotherapy. (The role of the drug in treating HBeAg negative disease is more difficult to define, because the treatment endpoints, particularly in the short term, are problematic.) The modelling presented by the Committee suggests that entecavir is also cost effective compared to lamivudine or adefovir. What the document does not address (due to the rapid pace of change in this field) is how entecavir compares to combination therapy with adefovir/lamivudine, or to monotherapy with the recently licensed nucleotide analogue tenofovir. There is currently inadequate evidence directly to compare either of these treatments with entecavir, although there are theoretical arguments which could favour the alternatives.

iii) We agree with the Committee that entecavir does have a role in the treatment of HBeAg positive chronic hepatitis B infection. However we do not believe that that role has been clearly defined, as alternative treatment strategies have not been fully evaluated. We also believe that it is too early to decide that entecavir does not have role in HBeAg negative disease, as this is very difficult to determine using short

term endpoints. We recommend that the STA on entecavir should at least make reference to the other alternatives to entecavir therapy (i.e. combination therapy, and tenofovir). We also reiterate our request for a full and comprehensive appraisal of the management of this complex and important infection.

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