Dear Christopher and Kate,

Comments on entecavir ACD:

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

The ACD summarises the clinical issues well, taking into account:

- the importance of potency of the medications; entecavir is amongst the best alongside telbivudine and tenofovir;
- the need for long term, possibly lifelong, therapy and the inevitable development of drug resistance when single agents are used; less with entecavir (negligible over 4 years) than the other drugs but probably significant over longer periods.

The evidence base is complete and the ACD summary takes this into account.

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?

I support the ERG and ACD view that we need to consider longer periods of treatment than the 2 year and 5 year periods for treatment (respectively for HBe +ve and –ve subjects) used by the manufacturer. The inability to come to a conclusion for recommendation in HBe –ve patients in general and, in particular, for patients with compensated cirrhosis is a problem at a clinical level because it is in the HBe-ve group that we are anticipating the need for lifelong therapy where the low incidence of resistance with entecavir is a major attraction, and in cirrhotics this is again a major attraction because with resistance the cirrhotic patient undergoes reactivation and is particularly vulnerable to decompensation because of the reduced capacity of the cirrhotic liver to regenerate after an exacerbation. The manufacturer should try to address this so that these groups are not deprived of the advantages of entecavir.

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?

Yes in HBe +ve subjects. In HBe-ve subjects the manufacturer should address the questions raised in section 1.3 – see above for my reasons.

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

It is worth bearing in mind that CHB is mainly a disease of ethnic minorities (Chinese, African, Asian and Eastern European) and even the currently relatively ineffective lamivudine has been shown to improve survival substantially. We can expect even better survival results with more potent drugs and lower resistance rates, such as entecavir, by projecting forward on the basis of the current surrogates of disease amelioration (ALT and histology) with entecavir and using the observed MR data with lamivudine (Liaw et al).

I hope this helps.

Yours sincerely