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BY E-MAIL

Dear Alana,

HEALTH TECHNOLOGY APPRAISAL – Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B

Thank you for the opportunity to comment on the Assessment Report produced by Southampton Health Technology Assessment Centre (SHTAC) for the above technology appraisal.

Overall, we believe that the report provides both a thorough and fair review of the available clinical and cost effectiveness evidence base. However, we have a small number of points of feedback and these are set out below.

Clinical Effectiveness

1) Published evidence

- The HBeAg positive data relating to pegylated interferon alfa-2a is described within the assessment report as unpublished. This data has appeared in abstract form (AASLD, 2004) and since the preparation of the assessment report the HBeAg positive clinical data has been published in full in the New England Journal of Medicine (Lau *et al*, June 2005). An electronic copy of the publication is provided as part of this response.

- Additionally one year follow up of the HBeAg negative study has now been presented at EASL in April 2005 and is also attached.

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2) Long term adefovir dipivoxil seroconversion rate

- The published HBeAg seroconversion rates with adefovir dipivoxil after 48 weeks of treatment are 12% (Marcellin[32]). Table 34 in the economic section describes the HBeAg seroconversion rate with adefovir dipivoxil to be 18%.

- The three year follow up data on clinical trial patients with adefovir dipivoxil are published in abstract form (Marcellin *et al*[43]). This data has not been subject to a peer review process and has the following limitations:

    - There is a progressive decrement in patient numbers at weeks 96 and 144. There is no adequate reason provided for this within the abstract, e.g. is this due to resistance? This potentially raises the issue of patient selection bias at these time points

    - The median ALT was 85 IU/L (2 X ULN) with no range provided. We believe it is essential to look at baseline ALT profiles and genotype splits in the patient cohorts at different time points as these are some of the variables which have been shown to influence seroconversion rates.

Cost Effectiveness

1) No clear reasons stated for higher QALYs achieved by adefovir dipivoxil relative to other comparators

- The economic model developed by SHTAC concludes that adefovir dipivoxil generates a greater number of QALYs compared to all other interventions in both the HBeAg positive and HbeAg negative populations. Tables 38 and 39 of the assessment report list an approximate 1.3 additional QALYs in HBeAg positive and 0.08 QALYs in HBeAg negative patients for adefovir dipivoxil compared to pegylated interferon alfa-2a.

- Upon examining the effectiveness assumptions listed in table 34, it is unclear how adefovir dipivoxil generates a higher number of QALYs within the model relative to pegylated interferon alfa-2a when pegylated interferon alfa-2a has a higher e-seroconversion rate (32% versus 18%) and an equivalent relapse rate to the CHB health state (9%). Additional detail on the clinical reasons and drivers for the large advantage in QALYs for adefovir dipivoxil should be scrutinised by the Appraisal Committee.

- At present one may only speculate that the reason for significantly larger QALYs being achieved by adefovir dipivoxil is explained by the longer term seroconversion rate assumptions within the SHTAC model. These assumptions are not currently stated within the description of the economic model. If the rates listed in the conference abstract referred to on page 67 within the clinical section (29% at week 96; 42% at week 144) are utilised in the model to represent long term seroconversion rates for adefovir dipivoxil, the methods of applying these data within the context of the SHTAC model should be made explicit for the Appraisal Committee. There is the possibility that the application of these seroconversion probabilities when estimating long term seroconversion may overestimate the long term effectiveness and hence the QALYs of adefovir dipivoxil.

2) Points of clarification on the Roche economic model

- P.112 The evaluation of the no treatment strategy does include the spontaneous seroconversion assumption within the Roche HBeAg positive model.

- P.113 adefovir dipivoxil patients similar to lamivudine patients in the model are assumed to remain on treatment for a 6 month consolidation period following seroconversion.

We hope that these comments are helpful for the Appraisal Committee.

Please do not hesitate to contact me if you require any further clarification or explanation of our feedback.

Yours sincerely.