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BY E-MAIL

Dear Chris,

SINGLE TECHNOLOGY APPRAISAL – Entecavir for the treatment of chronic hepatitis B

Thank you for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal. Our response is provided below using the four standard headings of response.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

Roche considers that all of the relevant evidence has largely been taken into account in the appraisal. However there are some exceptions:

- The model makes no mention of HBsAg negative disease seroconversion, which is regarded as the closest clinical outcome to a cure in the management of HBV. A long term follow up study by Marcellin et al (EASL 2008 - THE 43RD ANNUAL MEETING. Milan, Italy, April 23-27, 2008) shows that 4 years post treatment of HBeAg negative disease with 48 weeks of peginterferon alfa 2a there is an 11% HBsAg clearance – a rate of response not described in the literature for nucleoside analogues.

- The manufacturer's submission considers histological benefit for entecavir, telbivudine and lamivudine and but omits data for peginterferon alfa 2a in HBeAg negative disease. In a prospective randomised controlled trial, peginterferon alfa 2a demonstrated histological response in terms of improved necroinflammatory scores of 55% and improved fibrosis scores of 15% at 24 weeks of follow up after 48 weeks therapy (Marcellin et al NEJM, 2005).

- In the modelling for the antivirals, the assumption is that patients who achieve HBeAg seroconversion in year 1 would not receive therapy in year two – the justification is that this reflects the clinical trial data for entecavir. However, there is consensus that HBeAg serconversion induced by nucleoside analogues is not as durable as seroconversion brought about by interferons. Therefore, current clinical practice is evaluating a period of 'consolidation therapy' where antiviral therapy is extended for 6-12 months post seroconversion (Sherman et al Can j Gastro 2007; Papatheodordis et al The Lancet, 2007; Hoofnagle et al Hepatology 2007). Exclusion of this concept may result in an underestimation of the costs of nucleoside analogues. Roche note that scenario analysis was undertaken by the manufacturer with respect to consolidation therapy and this should potentially be considered as part of the base case analysis.

2 WHETHER 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

We would like to raise the following points

- Roche agrees with the ERG query on the use of a 2 year period of antiviral treatment assumption in the HBeAG-positive model as this is thought to be incorrect.
    - It is believed that in current clinical practice patients would spend longer on antiviral therapy than the two years modelled i.e. until post seroconversion consolidation (currently being evaluated in clinical practice) or treatment failure (when another antiviral would be used).
    - The 2 year assumption is a relative one for the antiviral agents but results in a bias against peginterferon alfa 2a which has an undisputed fixed duration of therapy of 48 weeks. Therefore an ICER of peginterferon alfa 2a compared to entecavir will be heavily skewed in favour of the latter.
    - Roche note the Appraisal Committee's reasoning that a short treatment duration is reasonable in HBeAg positive patients because a substantial proportion of patients can be expected to seroconvert. However Roche would draw the Committee's attention to the seroconversion rates estimated in year 1 and year 2 and used in the manufacturer's submission. Peginterferon alfa 2a is estimated to have the highest rates of seroconversion and only 18.3% of entecavir patients are estimated to seroconvert in year 1, and 10.4% in year 2. (Studies have shown that the average rate of spontaneous HBeAg seroconversion during the immune clearance phase is up to 10% per year (Liaw *et al*,. Gastroenterology 1983; 84: 216-219 & Lok *et al*.. Gastroenterology 1987; 92: 1839-1843)).

- As treatment would be expected to stop at seroconversion this means that the majority of patients would be expected to remain on treatment after year 2. This is not the case for peginterferon alfa 2a due to the fixed duration of therapy of 48 weeks. Therefore not including longer treatment durations for the antiviral agents' results in bias against peginterferon alfa 2a. Roche suggest that longer treatment durations are assumed for the antiviral agents in the base case. Data for entecavir has been presented over a four year treatment duration in HBeAg positive disease - S Han *et al*. Four-Year Entecavir Treatment in Nucleoside-Naive HBeAg(+) Patients: Results from Studies ETV-022 and -901 58th AASLD2007. Abstract 938.

- 48 weeks of treatment with peginterferon alfa 2a will generate a 32% rate (ITT) of HBeAg seroconversion at 24 weeks end of treatment follow up (Lau et al NEJM 352:26 2005). The manufacturer's submission states a 24.5% HBeAg seroconversion rate for peginterferon alfa 2a Vs. 18.3% for entecavir in one year. This comparison is not appropriate due to the immunomodulatory action of peginterferon alfa 2a, whereby the effects of 48 weeks therapy continue beyond treatment – hence the primary efficacy end point at which treatment is determined is six months post Rx – data from Korevaar *et al*, AASD 2007, based on long term follow up to standard interferon alfa describes the long term HBsAg seroconversion in HBeAg responders – by year 10 post treatment, this rate is 60%. Therefore when considering the effects of one year of treatment results for peginterferon alfa 2a should be considered at 24 weeks after the end of treatment. Roche would like to also draw the Appraisal Committee's attention to the fact that the confidence interval for seroconversion rates for HBeAg patients ranged between 15.4% and 21.4% for entecavir and so does not include the one year mean rate stated (24.5%) for peginterferon alfa 2a. The true seroconversion effect of 48 weeks of peginterferon alfa 2a treatment (32%) is higher and this suggests that peginterferon alfa 2a is likely to result in higher seroconversion rates for these patients, perhaps statistically significantly so.

- In the mixed treatment comparison the probability of response on any outcome measure was only estimated at year one for peginterferon alfa 2a. Given the arguments mentioned above, this will not reflect the true effectiveness of peginterferon alfa 2a.

- Roche agrees with the ERG query on the use of a 5 year period of antiviral treatment assumption in the HBeAg-negative model as this is thought to be incorrect.

    - The flaw in this assumption is that in clinical practice, patients with HBeAg negative disease will stay on antiviral therapy indefinitely (assuming that they do not develop resistance).
    - As with the HBeAg positive modelling, this assumption is a relative one for all the nucleoside analogues but represents a bias in terms of calculating the ICER vs peginterferon alfa 2a which has a defined treatment duration of 48 weeks.

- With regard to the modelling of peginterferon alfa 2a HBeAg negative patients switching to lamivudine:

    - Of those patients who have experienced a biological and virological response (approximately 43% <20,000 HBV DNA, 59% normalise ALT & 36% achieve a combined response after 48 weeks plus 24 weeks follow up) a proportion will remain off therapy indefinitely. Therefore it is inappropriate to assume that all patients go on to lamivudine at year three and are exposed to year 1 lamivudine resistance rates in the calculation of an ICER.

- In the ERG scenario analysis lifetime treatment duration was investigated for HBeAg-negative patients. The ICER for entecavir compared to peginterferon alfa 2a increases to £11,100 compared to the base case ICER of £7,511 (table 31). However this is based on an assumption that all peginterferon alfa 2a patients switch to lamivudine treatment (plus adefovir when resistance develops) in year 2 or year 3, depending on whether viral suppression had been achieved at the end of year 1. This adds substantially to the costs associated with initial peginterferon alfa 2a treatment and is not an appropriate assumption. In fact, a significant proportion of patients do not receive lamivudine after peginterferon alfa 2a due to the proportion of patients who experience durable viral suppression, normalisation of ALT and progressively HBsAg clearance. Data from Piratvisuth *et al* APASL 2007 describes the durable virological response fours years post treatment with peginterferon alfa 2a – suppression of HBV DNA to <2,000 IU/ml is 30%, 28%, 28% and 24% across the four follow up years respectively, 27% normalise ALT 4 years post treatment, 17% are HBV DNA <100/IU/ml and 11% clear HBsAg . This bias is relevant whether considering a 5-year or lifetime treatment period.

- In the ERG scenario analysis the results of assuming an increased treatment duration are only presented for entecavir compared to lamivudine in HBeAg positive patients (table 32). However, considering that the treatment duration of peginterferon alfa 2a is fixed at one year for these patients, and that only a proportion of these patients would receive lamivudine treatment in future

years it would be most relevant to also present results compared to peginterferon alfa 2a here. It is Roche's view that comparing entecavir to peginterferon alfa 2a over a lifetime period for HBeAg positive patients would demonstrate the cost effectiveness of peginterferon alfa 2a.

- The manufacturer's submission estimates normalising of ALT as 79% for entecavir Vs. 36% for peginterferon alfa 2a. This comparison is not appropriate due to the immunomodulatory action of peginterferon alfa 2a, whereby the effects of 48 weeks therapy increase over the end of treatment follow up – hence the primary efficacy end point at which treatment is determined is six months post treatment at which point 59% of patients have normalised their ALT.

- Roche agree with the ERG that the following claim made by the manufacturer is unjustified based on the results of the Mixed Treatment Comparison (MTC): "Entecavir is superior to pegylated interferon alpha 2a in nucleoside-naive patients in terms of viral suppression and ALT normalisation, and equivalent in terms of HBeAg seroconversion (HBeAG positive patients only, by definition), and has a lower rate of adverse events". Therefore the use of the MTC results in the economic model may not be accurate, particularly because the most relevant clinical data for peginterferon alfa 2a (6 months post treatment) was not collected in the MTC.

- A significant proportion of patients in the clinical setting are not treatment naive and are being managed for lamivudine resistance. An abstract presented at CDDW 2008 (S Fung *et al* SURVEILLANCE FOR HEPATITIS B VIRUS (HBV) ANTIVIRAL RESISTANCE (AVR) IN CLINICAL PRACTICE) identified 40% prevalence of the L180M in the analysis of treated patients. The manufacturer's submission models the ICER of entecavir vs. adefovir + lamivudine in HBeAg positive patients. With a 40% 4 year resistance (Colonno *et al* EASL 2007) for entecavir in lamivudine refractory patients. It would be meaningful to model the cost effectiveness of entecavir vs. peginterferon alfa 2a across both HBeAg positive and HBeAg negative lamivudine refractory patients. This is important because this group represents a significant proportion of chronic hepatitis B patients treated within the NHS.

3 WHETHER 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

Given the above issues highlighted in relation to key assumptions within the economic modelling, Roche suggest further sensitivity analysis is required before the current conclusion within the ACD that entecavir is cost effective compared to Peginterferon alfa 2a is confirmed. The issues outlined above demonstrate that the current evidence that has been considered by the Appraisal Committee is not fully complete with regard to the omission of important sensitivity analysis and therefore currently is not wholly a suitable basis for the preparation of guidance to the NHS.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

Not as far as we are aware.

We hope that our feedback is helpful to the Appraisal Committee in its subsequent deliberations.

Yours sincerely,