NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Entecavir for the treatment of chronic hepatitis B

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Comments from consultee organisations and nominated experts

Consultee	Comment	Response
Bristol Myers-Squibb	1. Summary Bristol-Myers Squibb (BMS) welcomes the preliminary recommendation from the Appraisal Committee (AC) that ETV is both cost and clinically effective for the treatment of HBeAg positive chronic hepatitis B (CHB) patients. BMS notes that both the Evidence Review Group (ERG) and the AC recognised the clinical effectiveness and value of ETV in the HBeAg negative population and is pleased to provide further clarification on the cost and clinical effectiveness of ETV in HBeAg negative patients as requested by the Committee: 1) The consideration of alternative treatment strategies in particular: a) Using a typical cohort of patients starting with ETV that represents NHS practice in terms of prevalence of existing active cirrhosis. b) The continuation of treatment with ETV when patients progress to compensated cirrhosis. c) Lifetime-treatment duration. 2) The relative effectiveness of ETV in people with compensated cirrhosis. 3) The relationship between the surrogate outcomes used and the final effectiveness outcomes of the model.	See response to detailed comments below

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	The revised BMS base case results show that ETV is cost-effective in HBeAg negative patients allowing for a mix of cirrhotic/non-cirrhotic patients starting treatment and when therapy is continued in patients who develop compensated cirrhosis, and lifetime treatment duration is considered. The incremental cost per QALY (Quality Adjusted Life Year) ratio for ETV in the revised base case is £20,463 when salvage therapy costs (omitted in the ERG scenario analysis) are applied to patients who develop resistance prior to developing compensated cirrhosis. Incorporating a mixed non-cirrhotic / cirrhotic patient population starting on therapy into the revised base case analysis, results in incremental cost per QALYs for ETV versus lamivudine ranging from £24,335 for a 90%:10% non-cirrhotic/cirrhotic split to £29,176 for a 80%:20% split. These incremental cost per QALYs reduce further when salvage therapy costs are included for all patients who develop resistance to between £17,083 and £19,023 for the 90%:10% and 80%:20% splits respectively.	Following consideration of the additional analyses presented (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee has decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
Bristol Myers-Squibb (continued)	BMS requests that the Appraisal Committee recommends entecavir in HBeAg negative patients, based on the supplemental analyses of cost effectiveness and the comments that follow in this response. BMS would first like to respond to the four questions posed by the Institute, followed by the detailed response to the ACD.	Comment noted
Bristol Myers-Squibb (continued)	i) Do you consider that all of the relevant evidence has been taken into account? In this response BMS has referred to two recently published conference abstracts reporting five year resistance rates for the 901 study referenced in the original submission and the results of a new study reporting resistance data for entecavir (ETV).	Comment noted

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	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? The summaries of clinical and cost effectiveness data in the Appraisal Consultation Document (ACD) are reasonable interpretations of the data presented in the original BMS submission. A revised base case cost effectiveness estimate based on alternative treatment strategies is provided by BMS for consideration by the AC. In this revised base case it is assumed that patients who become resistant to lamivudine therapy subsequently require add-on adefovir salvage therapy, as this is in line with clinical practice in the UK and previous NICE guidance. It is apparent that the ERG's scenario analysis (page 97 of the ERG report) for ETV in the HBeAg negative population omits salvage therapy costs for lamivudine resistant patients who develop compensated cirrhosis (CC). Instead, the ERG's calculation of treatment costs in the CC state rests upon the assumption that all patients would remain on lamivudine monotherapy regardless of resistance status. This is unlikely to be the case in actual clinical practice. This approach has introduced a significant bias into the ERG's estimates of cost effectiveness of ETV by underestimating the drug treatment costs for patients in the lamivudine arm following the development of resistance, and produced incremental cost effectiveness ratios (ICERs) that favour lamivudine over ETV. The ICERs estimated by the ERG are, therefore, neither an accurate nor a clinically reasonable reflection of the cost effectiveness of ETV relative to lamivudine.	Comment noted

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	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? BMS welcomes the provisional recommendation from the Appraisal Committee that ETV is both cost and clinically effective for the treatment of HBeAg positive CHB patients. However, BMS requests that the Appraisal Committee recommends entecavir in HBeAg negative patients. The additional analyses presented in this response show that ETV is a cost effective therapy in the HBeAg negative population based on lifetime treatment duration, continuation of treatment for patients who have developed CC, and a mixed cirrhotic/non-cirrhotic population starting therapy.	Following consideration of the additional analyses presented (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee has decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
Bristol Myers-Squibb (continued)	iv) Are there any equality related issues that need special consideration that are not covered in the ACD? None.	Comment noted
Bristol Myers-Squibb (continued)	2. Cost-Effectiveness of ETV in HBeAg Negative Patients In response to the request from the Appraisal Committee (AC) (section 1.3 of ACD), Bristol-Myers Squibb (BMS) has provided below further clarification on the cost effectiveness of entecavir (ETV) for the treatment of people with HBeAg-negative chronic hepatitis B (CHB) on the following issues: Consideration of two alternative treatment strategies in a revised base case: 1. Lifetime-treatment duration and continuation of treatment with ETV when patients progress to compensated cirrhosis (CC) 2. Treatment strategy above modified to include a mixed cohort of cirrhotic / non-cirrhotic patients starting with ETV to reflect NHS practice in terms of prevalence of existing active cirrhosis	

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	**2.1 Lifetime treatment (including compensated cirrhosis)** In revising the base case estimates of cost effectiveness for the HBeAg negative population, BMS has made a number of changes to the analysis presented in the original submission.	The committee noted the revised analysis presented by the manufacturer (see FAD 3.15 to 3.17 and 4.10 to 4.12)
Bristol Myers-Squibb (continued)	*Duration of therapy* Although there is evidence showing that virological remission can be maintained after therapy discontinuation in a selected subgroup of HBeAg-negative CHB patients successfully treated for 4 to 5 years, the optimal duration of therapy for these patients is still unknown. Lifetime duration of therapy was assumed, consistent with the assumptions of the Evidence Review Group (ERG) in their scenario analysis reported on page 97 of their report.	

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Bristol Myers-Squibb (continued)	*Continuation of therapy for compensated cirrhotic patients* To allow patients in the economic model to continue therapy once they have developed compensated cirrhosis (CC), the progression rate from compensated to decompensated cirrhosis (DCC) needs to be adjusted, as the rate used in the original submission represents an untreated rate of progression. As data on rates of progression from CC to DCC with ETV versus lamivudine do not exist, the 1.8% rate as suggested by the ERG (page 97 of ERG report) was used and progression is assumed to be independent of therapy. However, it must be emphasised that this progression rate is likely to significantly overestimate the incremental cost per QALY (Quality Adjusted Life Year) for ETV, as there is recent trial evidence showing that progression of cirrhosis in hepatitis B patients is linked with drug resistance. In this study of CHB patients with advanced fibrosis and cirrhosis, disease progression was assessed by a worsening in Child-Pugh scores and was observed in 7% of lamivudine-treated subjects with genotypic resistance (YMDD mutations) compared with less than 1% in lamivudine-treated patients without resistance. Thus the number of patients that experienced a progression of their cirrhosis was seven times higher amongst resistant compared with non-resistant patients. ETV is more likely to slow cirrhosis progression compared with lamivudine as it is associated with very low rates of resistance (approximately 1% of patients over 5 years)**Error! Bookmark not defined.** whereas lamivudine is associated with significantly higher (67% after 4 years) rates of genotypic resistance. However, for simplicity, the revised base case estimates assume the same rate of progression from compensated to decompensated cirrhosis (1.8%) for both ETV and lamivudine, and therefore underestimates the benefit of ETV.	See FAD 3.15 to 3.17 and 4.10 to 4.12

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	*Salvage therapy* In the revised base case, patients who become resistant and require salvage therapy before developing CC are assumed to continue on the same therapy once they develop CC. This assumption is consistent with clinical practice in the UK and previous NICE guidance, where adefovir is recommended for use in combination with lamivudine when treatment with lamivudine has resulted in resistance.**Error! Bookmark not defined.** Maintaining patients on salvage therapy in the CC state is especially important as the goal is to prevent progression to decompensation through sustained viral suppression and low resistance. Following clarification from the ERG (10th, 14th, 23rd April 2008), it appears that this assumption was not made in the ERG's scenario analysis (page 97 of the ERG report). In the ERG's analysis, patients on salvage therapy of lamivudine plus adefovir combination because they have developed resistance to lamivudine monotherapy prior to entering the CC health state, are incorrectly and inappropriately switched back to lamivudine monotherapy once they enter this state. The omission of salvage therapy costs in the ERG's scenario analysis, introduces a significant bias in favour of lamivudine into the cost effectiveness estimates.	

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Bristol Myers-Squibb (continued)	The cost of salvage therapy (an additional cost of £3,833 per patient per year) was incorporated into the model for patients who develop resistance prior to developing CC, by estimating an indicative mean drug cost for individuals in the model, based on the number of patients who become resistant and require salvage therapy at the end of each cycle before entering the CC state. As this analysis does not take into account patients who develop lamivudine resistance whilst in the CC state, an additional scenario analysis (Salvage costs for all resistant patients) was also undertaken, as these patients should also be treated with salvage therapy. This scenario analysis required splitting the existing CC state into two: a CC state for patients who become resistant to their first-line therapy and require salvage treatment; and a CC state for patients who are still receiving first line monotherapy and become resistant over time whilst in this state. This alternative approach allows for treatment costs in each arm to be more precisely estimated.	
Bristol Myers-Squibb (continued)	*Revised base case results* Table 1 presents the results for the revised base case analyses as well as the ERG estimates. Including the costs of salvage therapy for patients who become resistant prior to developing cirrhosis only reduces the ICER from £27,124 (ERG estimate) to £20,463 for the comparison of ETV to lamivudine. Splitting the compensated cirrhosis state into two states – resistant and non-resistant patients with compensated cirrhosis – reduces the ICER further to £15,531. **Table 1: Cost effectiveness of ETV compared with LVD assuming lifetime duration and continuation of treatment in cirrhotic patients** {not reproduced here}	The committee noted the revised analysis presented by the manufacturer (see FAD 3.15 to 3.17 and 4.10 to 4.12)

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	**2.2 Inclusion of mixed cirrhotic/non-cirrhotic patients starting therapy into revised base case** To provide further clarification to the AC on the cost effectiveness of ETV in HBeAg negative CHB patients, a mixed cirrhotic/non-cirrhotic population at baseline was modelled using the same methodology as used by the ERG. The efficacy of ETV in cirrhotic patients was assumed to be similar to that demonstrated in non-cirrhotic patients, as supported by the sub-analysis from the 027 trial shown in Table 2. The HBeAg negative model was re-run using a range of assumptions relating to the proportion of patients presenting with cirrhosis at treatment initiation. The non-cirrhotic to cirrhotic split was explored for the following scenarios - 100%/0%, 90%/10%, 85%/15%, 80%/20%. **Table 2: Percentage of patients with HBV-DNA<300 at Week 48 (027 trial)** {not reproduced here} The results of the revised base case including a mixed non-cirrhotic/cirrhotic population starting treatment, as well as the ERG's cost effectiveness estimates are presented in Table 3. The table shows that the revised base case estimates increase from £20,463 and £15,531 to £29,176 and £19,023 respectively, as the non-cirrhotic/cirrhotic mix increases from 100% non-cirrhotic to a mix of 80% non-cirrhotics and 20% cirrhotics. These ICERs indicate that ETV is a cost effective use of NHS resources. **Table 3: Cost effectiveness of ETV compared with LVD in a mixed cirrhotic and non-cirrhotic HBeAg negative population** {not reproduced here}	The committee noted these additional analyses (see FAD 3.16)

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	**3. Other comments** <u>ACD Section 4.9 – Relationship between surrogate outcomes used and the final effectiveness outcomes of the model</u> The ACD stated that the Committee would also welcome further information regarding the relationship between surrogate outcomes used in the model and the final effectiveness outcomes, and comparison of the model results with that observed in observational studies (section 4.9 of ACD). The use of HBV DNA levels as a surrogate marker for effectiveness is increasing in clinical practice. International and national clinical guidelines are increasingly referring to viral load as one of the criteria to initiate and monitor therapy. To help clarify this relationship, additional analyses are presented below of the number of events for both ETV and lamivudine, and the number of events avoided by treating with ETV. Results on final effectiveness outcomes of the model, i.e. number of cirrhosis and hepatocellular carcinoma cases, are reported in Table 4 for both the HBeAg positive and negative populations. All results correspond to the number of new events per 1,000 individuals. For the HBeAg negative population, lifetime treatment duration and continuation of treatment when patients progress to compensated cirrhosis (1.8% progression rate per year from compensated to decompensated cirrhosis for both ETV and lamivudine) was assumed in line with the ERG scenario analysis. In the HBeAg positive population, the base case was unchanged from BMS's original submission dated 26 November 2007. **Table 4: Estimated number of Cirrhosis and HCC events with ETV and LVD in both HBeAg negative and positive models** {not reproduced here}	The Committee noted this additional information see FAD 4.11

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	There is a dearth of long-term observational studies that correlate surrogate markers such as viral load to long-term outcomes, number of cases of cirrhosis and hepatocellular carcinoma. The largest natural history study to date, REVEAL-HBV, is a 13-year prospective, population-based cohort study in Taiwan of 3,653 CHB patients. This study showed that HBV DNA levels are an important predictor of the risk of HCC and cirrhosis. The results from the REVEAL-HBV study are corroborated by those in a smaller prospective study of 70 Caucasian Italians with a 25-year follow up. The number of cases of cirrhosis and hepatocellular carcinoma from these studies is presented in tables 5 and 6 below. **Table 5: Incidence rates for cirrhosis and HCC in individuals with CHB (reproduced from REVEAL-HBV)** {not reproduced here} The number of cases of cirrhosis and hepatocellular carcinoma from the Fattovich study is presented in table 6 below. **Table 6: Incidence rates for cirrhosis and HCC in individuals with CHB (reproduced from Fattovich et al)** {not reproduced here} In general, the incidence of cirrhosis and HCC cases reported in observational studies are higher than the incidence generated by the model for both populations. This would be expected as the observational studies reported in tables 5 and 6 analyse untreated patients who would be expected to have a higher incidence rate of both cirrhosis and HCC incidence than the treated patient cohorts analysed in the economic model.	The Committee noted this additional information see FAD 4.11

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Bristol Myers-Squibb (continued)	In the HBeAg positive model, individuals are treated for two years only and revert to the natural history of CHB for the remaining time in the model. Therefore, it would be expected that the incidence of cirrhosis and HCC cases from the observational studies would be closer to that predicted by the economic model for this population, as treatment is given for two years and not lifetime. In contrast, in the HBeAg negative model, patients are treated for lifetime and viral load is continually suppressed; therefore, a lower incidence of cirrhosis and HCC would be expected.	Comment noted.

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	ACD Section 4.6 – Resistance In section 4.6, the ACD stated that the low rates of resistance reported for ETV were biologically plausible. However, it is also stated that the Committee remained unconvinced that this low rate of resistance could be expected to be maintained over the long term. In the original submission, BMS submitted data on patients who were originally enrolled in the 022 and 027 studies and continued on ETV treatment in the 901 rollover study. These data showed that for patients treated with ETV for up to four years, there was a cumulative probability of virological breakthrough due to ETV genotypic resistance of less than 1.2%. BMS now has five year data on the same cohort of patients. These data shows that patients continue to demonstrate low resistance, with no additional patients reporting genotypic resistance. Thus, the cumulative rate of genotypic resistance at 5 years remains at 1.2% (Figure 1). **Figure 1: Cumulative probability of ETV resistance over 5 years in nucleoside-naïve cohort (HBeAg positive and HBeAg negative patients)** {not reproduced here} BMS recognizes that the resistance data from the 901 rollover study is not based on an intention to treat population, as responders were not followed up. However, there is no clinical reason to believe that the resistance rates in responders would be higher than that of partial and non-responders if they had likewise been followed-up for 5 years. The results of a recently-reported Japanese study independently confirm the findings from the 5 year resistance monitoring programme presented above. This study monitored resistance in a cohort of 66 nucleoside-naïve patients who received ETV (0.5mg) for 3 years. Only one patient showed evidence of ETV resistance substitutions at year 3 (1.7% cumulative probability).	Comments noted – See FAD 4.6

Consultee	Comment	Response
Bristol Myers-Squibb (continued)	ACD Section 7.2 – Proposed date for review of guidance BMS notes that the guidance on ETV is proposed to be considered for review in February 2009. However, BMS would suggest that this review date is too early since no significant new evidence is likely to be available at this point. CIC REMOVED. Therefore, BMS would like the review date for this guidance to be scheduled for 2012 when new data will be available and guidance on ETV can be meaningfully reviewed.	Review date has been set to coincide with the review of the multiple technology appraisal of adefovir dipivoxil and peginterferon alfa-2a.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage	Comment noted
Professor Howard Thomas, clinical expert nominated by the British Society of Gastroenterologists	1. 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	Comment noted

Consultee	Comment	Response
Prof Howard Thomas (continued)	2. 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.	Comment noted

Consultee	Comment	Response
Prof Howard Thomas (continued)	3. 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.	Comment noted. In response to the request from the Appraisal Committee, the manufacturer has provided a revised estimate of the cost effectiveness of ETV compared to lamivudine (LAM) in treatment of people with HBeAg-negative CHB to included: a) a lifetime-treatment duration and continuation of treatment with ETV when patients progress to compensated cirrhosis (CC) and b) a mixed cohort of cirrhotic / non-cirrhotic patients starting with ETV to reflect NHS practice in terms of prevalence of existing active cirrhosis
Prof Howard Thomas (continued)	4. 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).	Comment noted
Hepatitis B Foundation UK	➢ Hepatitis B Foundation UK is pleased to learn that NICE is minded to recommend entecavir in the e-antigen positive population.	Comment noted

Consultee	Comment	Response
Hepatitis B Foundation UK (continued)	➢ The Foundation is distressed to hear that NICE is minded to refuse entecavir in the e-antigen negative population. For e-negative patients there is little, in fact no, alternative for them if NICE is minded to refuse. This leads to the question of public health and safety when the UK will have a growing number of individuals not having their HBV DNA suppressed and yet living in the community until they require expensive treatments and therapy	Following consideration of the additional analyses presented by the manufacturer during consultation (see (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
Hepatitis B Foundation UK (continued)	The Foundation feels that NICE has to consider carefully the economic implications if entecavir is refused for e-negative patients for they will no doubt further down the patient pathway be given other probably less cost effective treatment. Meanwhile the UK continues to run the risk of onward transmission of the disease.	Following consideration of the additional analyses presented by the manufacturer during consultation (see (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

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Hepatitis B Foundation UK	The Foundation is concerned that these patients with potentially higher circulating rates of the virus may be denied treatment, as there is no alternative. The aim of therapy is to prevent progression of the disease to cirrhosis and end stage liver disease. If the disease has not progressed to cirrhosis then prevention of progression to advanced fibrosis or cirrhosis is desirable. There is a dearth of economic information concerning treatment of patients who require hospitalisation for cirrhosis and a liver transplant in the UK. However, in the USA costs of the former are estimated to be $14063 and the latter $89076. The Department of Health estimates the cost of a liver transplant in 2004 was some £18.370 and the recipient also requires a large number of expensive medicines and outpatient consultations as well as immunotherapy for life. In addition, there is the growing cost of treatment for hepatocellular carcinoma which again can have cost implications in terms of both surgery and chemotherapy. In determining the value of new drugs for the treatment of chronic hepatitis B, drug acquisition must be balanced against expected benefits in morbidity and mortality and cost avoidance from disease progression. Progression can be halted if HBV DNA remains suppressed and resistance or relapse do not occur. It is well known that resistance develops in patients receiving therapy such as lamivudine, with 80% becoming resistant in five years. With the drug adefovir resistance has also developed, with 80% of patients developing resistance within five years.	Following consideration of the additional analyses presented by the manufacturer during consultation (see (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
Royal College of Nursing	Nurses working in this area of health have reviewed this document. The consultation document is comprehensive. There is no further information to add to the proposals in the Appraisal Consultation Document.	Comment noted
South Asian Health Foundation	I am happy with the NICE technology appraisal document on Entecavir for the treatment of chronic hepatitis B. I have no specific comments to add.	Comment noted

Consultee	Comment	Response
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation. However, we do support NICE's ongoing appraisal of new treatments for chronic hepatitis B but believe that these should be looked at together, along with the existing NICE guidance on treatment of chronic hepatitis B and clinical management guidelines produced.	Comment noted
Royal College of Physicians	i) Do you consider that all of the relevant evidence has been taken into account? The most appropriate place for entecavir in the pathway of care of hepatitis B is to suppress HBV DNA replication in patients with ongoing evidence of HBV replication, raised serum ALT and evidence of advancing disease. Entecavir could be used more effectively than lamivudine for patients with raised serum aminotransferases (> 2x the ULN) and active levels of HBV DNA replication, (> 10^5 copies/ml) as viral suppression is more effective in this group, and resistance rates are far lower. This was demonstrable in both HBeAg positive and negative patients. It is important to reduce levels of replication in both HBeAg positive and negative patients with evidence of active HBV replication; lamivudine is currently 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 negative patients in the UK, although so recommended by NICE. This is largely related to patient choice, given the side effect profile of interferon, and the high relapse rates observed in this group. Pegylated interferon is often contraindicated in patients with cirrhosis and is problematical in patients with decompensated cirrhosis. Entecavir leads to rapid viral suppression low rates of resistance, and effective suppression of HBV DNA replication in both HBeAg positive and negative patients, and would be considered for treatment of both these groups of patients, with HBV DNA levels of > 10^5 copies /ml.	Following consideration of the additional analyses presented by the manufacturer during consultation (see (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee has decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

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Royal College of Physicians (continued)	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? The ICER for treating HBeAg negative patients are noted; the differential ERV probability analysis of 4% for entecavir being cost effective at a willingness to pay of £20,000 and 40% at a willingness to pay of £30,000 when compensated cirrhosis is also considered is puzzling given the responsiveness of patients with cirrhosis, most of whom have lower levels of HBV DNA and are HBeAg negative. The structural elements of the model including cirrhosis need re-examination	During the consultation period, the manufacturer submitted revised cost effectiveness estimates for the HBeAg negative population at the request of the appraisal committee. See FAD 3.15
Royal College of Physicians (continued)	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 ALT in large cohorts of Chinese patients and the subsequent risk of cirrhosis and HCC. Whilst incomplete, these date indicate the risk of persistent HBV infection to infected individuals, which may change existing equations for modelling progression. I note the ERV groups' sensitivity analysis using different utility values. Caution should be interpreted in using transition probabilities in current Markov models; the majority of Asian patients who develop decompensated cirrhosis or HCC are HBeAg-negative, and treatment is indicated to suppress levels of replication in these patients at risk.	Comment noted

Consultee	Comment	Response
Royal College of Physicians (continued)	The majority view is that clinicians regard this drug as a valuable addition to our treatment options. The very low resistance rates will allow a reduction in the prevalence of resistant viral strains and will permit prolonged monotherapy.	Following consideration of the additional analyses presented by the manufacturer during consultation (see (see FAD 3.15 to 3.17 and 4.10 to 4.12) the Committee decided to recommend entecavir, as an option for the treatment of people with chronic HBeAg positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
Royal College of Physicians (continued)	We are however surprised to find that the calculations show the drug to be non-cost effective for HBeAg disease. Many clinicians are now using lamivudine + adefovir as first line therapy for the majority of patients with this condition. 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.	Comment noted
Royal College of Physicians (continued)	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. Sequential monotherapy is a clinically dangerous strategy in patients with cirrhosis because of the risk of exacerbation. This will apply equally to HBeAg positive patients and HBeAg negative patients with high levels of HBV replication (> 10^5 copies/ml).	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg-positive or HBeAg-negative hepatitis B.

Consultee	Comment	Response
Royal College of Physicians (continued)	Since entecavir is cheaper than the current combinations the clinical community is surprised by the results of the analysis and it would be helpful to look into the cost effectiveness of entecavir compared to a large proportion of patients receiving combination therapy. In particular a review of the cost effectiveness calculations in patients with cirrhosis (the vast majority of whom receive combination therapy ab initio) would be helpful.	Comment noted
Royal College of Physicians (continued)	We note that further data on the cost effectiveness of entecavir in patients with cirrhosis has been requested and we hope that this will provide the evidence required to allow a positive opinion for patients with HBeAg negative disease	See above
Royal College of Physicians (continued)	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? We note the ERV critique of the decision problem not to include patients with advanced liver disease. It is crucial that safety and efficacy data are obtained in this group, who require rapid and effective suppression of HBV replication. It is likely that requests to use this agent in patients with advanced liver disease "decompensated liver disease" will understandably be made, in order to rapidly reduce HBV replication and improve liver function, or to suppress viraemia prior to liver transplantation to prevent recurrence. The most appropriate place for entecavir in the pathway of care of hepatitis B is to suppress HBV DNA replication in patients with ongoing evidence of HBV replication, raised serum ALT and evidence of advancing or advanced disease. Entecavir could be used more effectively than lamivudine or lamivudine and entecavir in combination for patients with raised serum aminotransferases (> 2x the ULN) and active levels of HBV DNA replication, (> 10^5 copies/ml) as viral suppression is more effective in this group, and resistance rates are far lower.	Comment noted. Entecavir is not licensed for use in decompensated disease and has therefore not been appraised in this indication.

Consultee	Comment	Response
Royal College of Physicians (continued)	iv) Are there any equality related issues that need special consideration that are not covered in the ACD? Importantly, entecavir is an effective treatment of hepatitis B with ongoing viral replication, and the economic data presented, which will potentially restrict the drug to patients with only HBeAg in serum, is not clinically meaningful in our current state of knowledge given that patients should be categorised by age, stage of disease, serum ALT, HBV DNA levels in addition to HBeAg status.	Comment noted
British Infection Society	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.	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg positive or HBeAg-negative hepatitis B. Comment noted

Consultee	Comment	Response
British Infection Society (continued)	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	Comment noted
British Infection Society (continued)	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.	Tenofovir has been provisionally referred in the 17th wave and will be appraised following formal referral.

Consultee	Comment	Response
British Infection Society (continued)	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	Comment noted
British Infection Society (continued)	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).	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg positive or HBeAg-negative hepatitis B.

Consultee	Comment	Response
British Infection Society (continued)	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.	Comment noted. The Final scope issued by NICE specified that entecavir should be compared to interferon alfa-2a interferon alfa-2b, peginterferon-2a, lamivudine, adefovir dipivoxil and telbivudine. The manufacturer compare entecavir to each of these therapies separately. Tenofovir was not licensed for treatment of chronic hepatitis B at the start of the appraisal and therefore was not included as comparator.
British Infection Society (continued)	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.	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg positive or HBeAg-negative hepatitis B.

Comments from commentator organisations

Commentator	Comment	Response
Roche	*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	Comment noted The Committee heard from the clinical experts that the current consensus is that the goal of treating patients with HBeAg-negative chronic hepatitis B is viral suppression. This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg-positive or HBeAg-negative hepatitis B and that entecavir is recommended as an option where antiviral treatment is indicated. First-line use of peginterferon alfa 2a as recommended in TA96 remains an option. This appraisal did not compare sequential treatment strategies.
Roche (continued)	• 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).	Comment noted

Commentator	Comment	Response
Roche (continued)	• 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. (Commercial in Confidence text removed here)	Comment noted
Roche (continued)	• 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. o 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). o 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.	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg-positive or HBeAg-negative hepatitis B and that entecavir is recommended as an option where *antiviral* treatment is indicated. First-line use of peginterferon alfa 2a as recommended in TA96 remains an option. This appraisal did not compare sequential treatment strategies

Commentator	Comment	Response
Roche (continued)	o 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)).	Comment noted
Roche (continued)	o 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.	Comment noted

Commentator	Comment	Response
Roche (continued)	• 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.	Comment noted
Roche (continued)	• 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.	Comment noted

Commentator	Comment	Response
Roche (continued)	• 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). o 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	During the consultation period, the manufacturer submitted revised cost effectiveness estimates for the HBeAg negative patient population at the request of the appraisal committee. This revised model considered lifetime treatment (see FAD 3.15).
Roche (continued)	• With regard to the modelling of peginterferon alfa 2a HBeAg negative patients switching to lamivudine: o 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.	Comment noted

Commentator	Comment	Response
Roche (continued)	• 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.	Comment noted
Roche (continued)	• 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.	

Commentator	Comment	Response
Roche (continued)	• 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 (continued)	• 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.	Comment noted
Roche (continued)	• 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.	Comment noted

Commentator	Comment	Response
Roche (continued)	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.	Comment noted
Roche (continued)	Not as far as we are aware.	Comment noted
Gilead	1. As noted by the committee we agree that the assumptions made in the manufacturer's model regarding the duration of therapy do not reflect clinical practice: • The majority of HBeAg positive patients would spend significantly longer on antiviral therapy than the two years suggested in the model. If a patient has achieved HBeAg seroconversion at 2 years they would receive a further 6-12 months of consolidation therapy and those who hadn't seroconverted would continue on treatment until failure (when another antiviral would be used). • In the model the manufacturer assumes that patients who achieve HBeAg seroconversion in year 1 would not receive therapy in year two, again in reality patients would receive consolidation therapy for at least 6-12 months. • The assumption that HBeAg negative patients receive only 5 years of antiviral treatment is incorrect. In clinical practice patients will remain on therapy until HBsAg loss/Seroconversion or treatment failure.	Comment noted.
Gilead (continued)	2. The analysis in LAM-refractory patients omitted adefovir monotherapy, which is a key comparator and is less costly than entecavir.	Comment noted.

Commentator	Comment	Response
Gilead (continued)	3. The analysis in LAM-refractory patients used an overly pessimistic estimate of the efficacy of adefovir plus lamivudine. Trials on adefovir plus lamivudine in patients with more severe disease show adefovir salvage therapy to produce substantial benefits, which are considerably higher than those assumed.[1]	Comment noted
Gilead (continued)	4. With the exception of commercial in confidence data, it would have been useful to be able to view the appendices of the submission in order to assess whether the inclusion criteria used, studies identified and statistical methods employed were appropriate.	Comment noted
SHTAC	Point 3.11 - Suggest removing the words 'both comparators' from the end of the sentence as the (single) comparator is the combination of adefovir and lamivudine, rather than the two separately.	The wording has been amended for the FAD
SHTAC (continued)	Point 3.12, line six please add 'scenario' between 'exploratory' and 'analyses'.	The wording has been amended for the FAD
SHTAC (continued)	Point 3.13 line 1, and Point 3.14 line 3, should be scenario rather than sensitivity analyses	The wording has been amended for the FAD
SHTAC (continued)	Point 4.7, page 14 sentence "The Committee agreed with the view that the model of HBeAg-positive chronic hepatitis B could be limited to a short treatment duration because a significant proportion of people could be expected to experience seroconversion and thus stop receiving treatment. The term 'significant' may be a bit of an over-statement. In the model in the entecavir arm it is assumed that 18% seroconvert in the 1st year and 10% seroconvert in the 2nd year. Even assuming that nobody seroreverts, less than 30% of patients would not constitute a significant proportion to terminate treatment.	The wording has been amended for the FAD

Commentator	Comment	Response
SHTAC (continued)	Point 4.8, line 12 suggest add 'scenario' between 'exploratory' and 'analyses'	The wording has been amended for the FAD
SHTAC (continued)	spotted a slight ambiguity in the paragraph 3.13 on page 10 of the entecavir ACD . We would like to suggest the following small amendments, as shown in red below: "The ERG also conducted exploratory scenario analyses of the HBeAg-negative model assuming a lifetime treatment duration. In this scenario patients who progressed to compensated cirrhosis continued receiving treatment unless (or until) they develop decompensated cirrhosis. The same rate of progression to decompensated cirrhosis was assumed for all alternative treatments (1.8% per year based on the estimate used for lamivudine in the previous technology appraisal of adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B – see section 6 below). This resulted in an ICER of £27,124 per QALY gained, when comparing entecavir with lamivudine".	The wording has been amended for the FAD

Web comments

Commentator	Comment	Response
NHS professional 1	Comment on Section 4: Consideration of the evidence There are a number of invalid assumptions in the ERG model used to calculate the cost effectiveness of entecavir in patients with HBeAg negative chronic HBV infection. Patients on effective treatment do not progress to cirrhosis but patients on lamivudine to progress either because of failure to suppress the virus or due to the emergence of viral resistance. As a result NO competent clinician would start a patient with cirrhosis or a patient with high viral load on lamivudine monotherapy. This is, of course entirely consistent with NICE TA96. In fact the ERG pointed out these errors to the modellers but the information appears to have been ignored. Lifetime treatment duration cannot be assumed. Some patients on nucleoside analogues can be with withdrawn safely from treatment but we do not have accurate data to guide treatment withdrawal at present	This guidance does not represent a definitive statement regarding the appropriate place of entecavir in the pathway of care of people with chronic HBeAg-positive or HBeAg-negative hepatitis B.