NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Telbivudine for the treatment of chronic hepatitis B

Response to consultee, commentator and public comments on the ACD

Comments from consultee organisations and nominated experts

Consultee	Comments	Response
Novartis	**Section A: Clinical Data** Section 3.6 of the ACD summarises the comments of the ERG and expert advisors regarding the results of the GLOBE trial. Novartis' main concerns regarding these comments are summarised below and then presented in detail. 1. The GLOBE trial is the largest ever trial in Hepatitis B, based on accepted endpoints, and the only trial to provide an analysis in a true intention to treat population. Consequently, the results are of clinical significance. 2. The rationale for calculating an absolute difference of only 2 percentage points is flawed. 3. The virological breakthrough at two years under telbivudine treatment is not unduly high compared to other drugs in this class and it is assumed that the comments relate only to a comparison with entecavir. 4. Clarity is provided over the power of the study for analysis of subpopulations i) Subgroup defined by race ii) Subgroup defined by elevated ALT 5. The HBeAg positive and HBeAg negative cohorts were analysed separately, according to pre-defined criteria and, therefore, neither is influenced by the results of the other. 6. Both histological *and* biochemical markers are relevant to the treatment decision.	Comments noted.

Consultee	Comments	Response
Novartis (continued)	**1. The GLOBE trial is the largest ever trial in Hepatitis B, based on accepted endpoints, and the only trial to provide an analysis in a true intention to treat population at 2 years. Consequently, the results are of clinical significance.** The ERG acknowledged the statistical significance of the GLOBE results but questioned their clinical significance. The relevance of the outcomes assessed in this trial to the clinical benefits experienced by patients was discussed in section 5.9.1 of the original submission. 5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice. *"The evidence from the pivotal study, GLOBE [45], demonstrates the significant benefits of telbivudine on the key outcomes of interest in the treatment of CHB.* *Chronic hepatitis B is a lifelong condition with serious clinical consequences that evolve over many years. Active disease progression ultimately leads to liver inflammation with associated morbidity, cirrhosis, decompensated liver failure, hepatocellular carcinoma and death. Few of these sequelae are appropriate for study in the setting of clinical trials, and indeed data from studies exceeding 5 years duration are rare. Therefore interventional trials invariably rely on surrogate endpoints (e.g. viral DNA levels; seroconversion) together with more direct evidence of disease activity and progression, namely ALT elevation, histologic evidence of inflammation and fibrosis. The correlation of both surrogate and direct measures with disease progression and outcomes has been determined in long-term observational studies with conclusive results [46, 47]. Thus HBV DNA is widely accepted as a surrogate for disease activity and an elevated viral load as a predictor of acute inflammation, progressive liver pathology and the consequent risks of fibrosis, cirrhosis and hepatocellular carcinoma.* *In summary, although the incidence of serious complications of CHB was low in the 2 year GLOBE study itself, the endpoints that were evaluated in the trial are internationally recognised as valid predictors of clinical outcome."*	Comments noted. See FAD sections 4.6 and 4.7

Consultee	Comments	Response
Novartis (continued)	In common with all other trials of therapeutic agents in CHB, the duration of treatment and follow-up are not sufficient to detect a measurable effect on the ultimate consequences of HBV infection, namely: cirrhosis of the liver decompensated liver failure and hepatocellular carcinoma. Therefore, in order to evaluate responses to treatment, indicators of disease activity and progression are measured as surrogate markers: Liver histopathology; HBV DNA as a measure of viral load and replication; HBsAg and HBeAg/Ab to detect seroconversion and serum transaminase levels as a biochemical marker of liver inflammation and damage.	The Committee considered the possible relationship between surrogate outcomes and long term clinical effects in making the decision. See FAD sections 4.2 and 4.4
Novartis (continued)	These endpoints are all recognised indicators of clinical disease widely used in therapeutic trials in CHB and are the self-same disease markers employed in the assessment of clinical and economic effectiveness of Peginterferon alpha-2a and adefovir dipivoxil in the earlier NICE guidance on Chronic Hepatitis B (Shepherd et al 2006; TA 96). The application of these endpoints, either singly or as a composite, for the independent analysis of HBeAg-positive and -negative populations in the GLOBE trial is entirely appropriate and the results are clinically relevant. In addition, GLOBE is the largest clinical trial of therapeutic agents in chronic hepatitis B conducted to date and remains the only study of CHB treatment that provides full ITT population analysis at 2 years. GLOBE was adequately powered for the analysis of both HBeAg-positive and HBeAg-negative patients as discrete groups or as a single population provided certain criteria were met for pooling the data. It compared telbivudine against lamivudine. This was the standard-of-care nucleoside agent available at the time of study design (2002) and remains the most commonly prescribed first line agent in the UK and across Europe. The outcomes measured were in keeping with former and current treatment guidelines (e.g. AASLD, APASL and EASL). Compared with any other pivotal clinical trial in CHB the GLOBE study was performed to a high standard, unrivalled in terms of size, design, integrity and statistical rigour up to 2 years ITT analysis. We therefore believe that it is very clinically relevant to UK patients.	Comments noted. See FAD section 4.4 and 4.5

Consultee	Comments	Response
Novartis (continued)	**2. The rationale for calculating an absolute difference of only 2 percentage points is flawed.** The ERG noted that the clinical significance of the differences between treatments was uncertain, observing that: "When the proportion of patients who discontinued treatment due to disease progression or lack of efficacy (0.8% versus 2.6% for telbivudine and lamivudine respectively) were considered in the analysis of the trial outcomes, there is an absolute difference of only about 2 percentage points for telbivudine over lamivudine." Although an explanation of the calculation was not provided, the small absolute difference of 2% appears to represent the difference in the proportion of patients discontinuing treatment for reasons of disease progression or lack of efficacy. From Figure 4 in our submission (p33) these numbers would be 6/680 (0.88%) for telbivudine and 18/687 (2.6%) for lamivudine, yielding a difference of approximately 2% between the treatment groups, based on observations in a total of 24 patients. Analysis of this specific group of patients was neither envisaged nor included in the study plan and does not provide robust information of relevance to the decision problem. Patients in this subgroup already classify as treatment failures within the current analysis which also incorporates the other 1343 patients of the ITT population. Consequently, the statement from the ERG appears to suggest that a comparison of the proportions of patients who discontinued drug due to treatment failure (i.e. disease progression or lack of efficacy) will provide a more meaningful assessment of clinical benefit than the endpoints assessed in the present analysis. In response, we would contest this approach since it based on a total of 24 patients (6 telbivudine: 18 lamivudine), whereas the current analysis is based in the ITT population of 1376 patients and already includes the 24 patients mentioned above (as failures). Therefore, the results as presented in the original submission provide a comprehensive analysis of the data.	Comments noted. The Committee considered the efficacy differences across all relevant health outcomes specified in the appraisal. See also FAD section 4.4, 4.5 and 4.6

Consultee	Comments	Response
Novartis (continued)	**3. The virological breakthrough at two years under telbivudine treatment is not unduly high compared to other drugs in this class and it is assumed that the comments relate only to a comparison with entecavir.** This statement is drawn from the ERG report. Under section 3.3.1.6, the degree of viral rebound seen at 2 years with telbivudine was, in the opinion of the ERG's expert advisor, "unacceptably high". This opinion was reiterated in the summary (3.4), where the ERG's clinical advisor stressed that a virological breakthrough of 28.6% [for telbivudine] at two years was unacceptably high at a clinical level. However, these statements were made without giving any terms of reference for the comparison. The report did not further qualify these observations by reference to any hypothetical or documented "acceptable" upper limit for the incidence of viral rebound, nor did it cite data for any drug delivering a reduced and acceptable breakthrough rate after two years' treatment. Therefore, in the absence of definitive information on the point of reference, it is assumed that viral rebound rates for telbivudine were compared with those reported for entecavir monotherapy or for experimental strategies using combinations of antiviral drugs. The following paragraphs describe the limited data available to compare viral breakthrough on telbivudine and entecavir monotherapies. RCT data comparing combination therapies are even more scarce and beyond the scope/remit of this STA.	Comments noted. The Committee based their decision on estimates of effectiveness across all the relevant clinical outcomes. See FAD section 4.4 to 4.7
Novartis (continued)	Virological breakthrough or rebound is an issue of key interest to clinical specialists since it potentially limits treatment options. Yet, the clinical consequences of viral rebound have not been systematically studied in terms of consequent patient morbidity and mortality. Any comparison of virological breakthrough rates for entecavir and telbivudine is confounded by the absence of RCT trial data directly comparing these two drugs. It should be stressed that comparisons of data taken from different trials should be treated with caution, and interpreted with full appreciation of the similarities and differences in trial design, particularly in terms of the duration of treatment and composition of the populations at time of analysis. The pivotal entecavir trials 022 and 027 identified in our original submission (Table 12 p 56), shared similar designs, populations, endpoints and comparator with the GLOBE trial for the first year of treatment only. The common features and differences have been described in our original submission (5.6 Characteristics of the RCTs). Given the similarities of the trials and the common definition for virological rebound it seems permissible to compare the breakthrough rates in entecavir and telbivudine treated patients at 48 weeks of treatment (Table 1).	Comments noted. .

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Novartis (continued)	Chang et al (2006) reported virologic rebound in 2% (6/354) of HBeAg-positive entecavir-treated CHB patients versus 18% (63/355) of the lamivudine-treated patients during the first year of treatment. Lai et al (2006) reported virologic rebound in 2% (5/325) of the HBeAg negative entecavir-treated patients versus 8% (25/313) of the lamivudine-treated patients by week 48. In the GLOBE trial, virological breakthrough occurred in 3.4% (15/438) of HBeAg-positive patients and 2.1% (4/192) of HBeAg-negative patients receiving telbivudine, compared to 10.4% (46/442) and 8.5% (16/187) respectively in the lamivudine groups, experienced virologic breakthrough. **Table 1: Summary of virological breakthrough results at 48 weeks in the pivotal entecavir and telbivudine studies** (not reproduced here)	Comments noted.
Novartis (continued)	At one year, the incidence of virological rebound in the HbeAg-positive patients treated with telbivudine (6%) and entecavir (2%) are similar, differing by only a few percentage points while the HbeAg-negative patient groups exhibited identical breakthrough rates at 2%. Virological rebound rates on lamivudine were similar across trials for the HbeAg-positive (15-18%) and HbeAg-negative patients (8-13%), confirming the comparability/consistency of the study designs and methodology. Based on analyses of ITT populations, the few percentage points difference is unlikely to be of clinical relevance. Any meaningful comparison of virological breakthrough results for telbivudine and entecavir beyond 1 year would be confounded by fundamental differences in study design. On completion of 52-weeks therapy in entecavir studies 022 and 027 patients either stopped therapy or continued blinded treatment according to protocol defined patient management criteria. Only patients who showed an intermediate ”response” were allowed to continue in the second year of the study, while ”responders” and ”non-responders” discontinued treatment. Thus, 31% of the entecavir group in the HbeAg-positive study (study 022) and 85% of the entecavir group in the HbeAg-negative study (study 027) were discontinued from further treatment in year 2. Since the definition for ”non responders” was based on the degree of HBV DNA suppression observed at 48 weeks, the effect of this process was to discontinue entecavir in that group of patients who had shown inadequate viral suppression in the first year (i.e. the group that are at greatest risk of virological breakthrough). Thus, the credibility of entecavir data for virological breakthrough at 2 years is compromised by the bias inherent in this selection procedure	Comments noted.

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Novartis (continued)	In contrast, in the telbivudine study (GLOBE 007) there were no protocol defined criteria prohibiting entry to the second year of treatment. Over the 2 year study period, no patients discontinued telbivudine for disease progression and only 6/680 patients discontinued for lack of efficacy. The GLOBE study, therefore, provides a true indication of virological breakthrough in the ITT population at 1 and 2 years of treatment. The 2 year results of GLOBE indicate virological breakthrough in the HbeAg-positive cohort as 28.6% (131/458) and 45.5% (211/463) for telbivudine and lamivudine respectively. In the HbeAg-negative cohort, breakthrough rates at 2 years were 12.2% (27/222) and 30.4% (68/224) for telbivudine and lamivudine, respectively. Notwithstanding the flaws in the rebound data for entecavir, Gish et al (2007) have reported a total of 13 patients from entecavir study 022 (HbeAg-positive) who experienced virological rebound over the 2 years of treatment in a selected subgroup of the original population. Discounting the 6 breakthroughs in year 1, this indicates an additional 7/243 (3%) in year 2 of treatment. Cumulative virological breakthrough for the lamivudine group (n=164) maintained on therapy into year 2 was not reported in this paper. No published report has been found for the 2 year results from the HbeAg-negative trial (027) in which only 15% of patients continued entecavir treatment into the second year. Referring to the limitations of their data at 2 years, the authors commented " *After week 52, it is not possible to provide an assessment in which all patients who originally started treatment are accounted for at a single time point under uniform treatment conditions. Therefore, the results from this study cannot be compared directly with other studies that evaluate continuous treatment in all patients through 2 years…" Gish et al 2007.* Given the similarities in reported virological breakthrough rates at one year for telbivudine and entecavir in the randomised trials and the lack of complete 2 year data for entecavir, it is extremely difficult to draw conclusions regarding the long term comparative rates of virological breakthrough and resistance.	Comments noted.

Consultee	Comments	Response
Novartis (continued)	**4. Clarity is provided over the power of the study for analysis of subpopulations** In several sections of the ACD, concerns are raised over the statistical integrity of the study and, in particular, the power of the study to detect differences in several subgroups presented in the MS. Summarised in 3.6, these subgroups include patients defined by race and serum ALT levels. The following paragraphs are to clarify the planned sample sizes, the criteria for stratification, and the definitions of populations defined by ALT level, and to address any misunderstanding over pre-planned and post hoc populations and analyses. **Statistical design and power calculations**: The GLOBE study was designed with the statistical power to detect the pre-defined efficacy parameters in both the HBeAg-positive and HBeAg-negative patients when analysed as separate groups (Table 2). Patients were stratified on HBeAg status at the time of randomisation to ensure balanced distribution to the treatment arms. **Table 2. Power Calculations for Efficacy Parameters** (not reproduced here)	Comments noted. The Committee had no concerns about the statistical integrity of the ITT population in the GLOBE trial. The concerns raised relate to the statistical integrity of the exploratory analysis of subgroups defined by serum ALT levels and their clinical relevance. See FAD section 4.6, 4.7 and 4.11

Consultee	Comments	Response
Novartis (continued)	The study design was intended to demonstrate effects in both HBeAg positive and HBeAg negative subpopulations or in the pooled population, if trends in the subpopulations warranted pooling. The primary end point was assessed using a three-step method: First, both HBeAg subpopulations were analysed separately with an alpha-level of 0.04 (95.68% confidence interval). If both subpopulations met the non-inferiority criteria (i.e., if confidence intervals for the treatment difference exceeded –15%), treatments would be compared for superiority within each subpopulation. If statistical significance was not established within both HBeAg subpopulations, a statistical test for interaction between the treatment group and HBeAg subpopulations was planned, with significance defined at the alpha level of 0.15. If no significant interaction was revealed within each patient subpopulation, a pooled statistical analysis for the overall patient population would be performed using an alpha-level of 0.000933. The primary endpoint of therapeutic response and the key secondary efficacy endpoint of histologic response, both at Week 52, were analysed using the 3-step statistical procedure (as outlined above) to control for the overall type I error. For both HBeAg-positive and HBeAg-negative patients, both therapeutic response and histologic response met the non-inferiority criteria at Week 52. Within the 3-step procedure, non-inferiority can therefore be claimed for HBeAg-positive and HBeAg-negative patients without performing a pooled analysis. However, the analysis results also showed a stronger treatment effect in HBeAg-positive patients (superiority) than HBeAg-negative (non-inferiority) for both the therapeutic response and histologic response, which showed a statistically significant treatment and HBeAg status interaction [P=0.0315].	Comments noted. See FAD 4.11
Novartis (continued)	**4 i) Subgroup defined by race** The GLOBE study was not prospectively powered to detect treatment differences in racial subgroups. Analyses conducted were only performed at an exploratory level. The tables of outcomes in racial subgroups were included in our Submission (MS table 3 and 4) as part of section 5.3.6 (Critical appraisal of relevant RCTs) in response to the question “How do the included RCT participants compare with patients that are likely to receive the intervention in the UK“. The data were included in anticipation of questions regarding the racial mix and its applicability to patients within the UK enabling the ERG to consider and acknowledge the GLOBE study population as representative of CHB patients in the UK.	Comments noted.

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Novartis (continued)	**4 ii) Subgroups defined by serum ALT level** Serum alanine transaminase (ALT) is a biochemical marker of inflammatory liver damage. Raised ALT levels usually mirror exacerbations of viral hepatitis and, when combined with other clinical features, are a consideration in the decision to commence treatment. In the GLOBE study, ALT ranges or thresholds were specified at entry to the study (1.3-10 x ULN) as a basis for stratification (< or > 2.5 x ULN), as a measure of efficacy (normalisation,=<1 x ULN) and to define a treatment eligible subpopulation for exploratory efficacy analysis (>2 x ULN). In addition, the clinical data selected to populate the models for the cost effectiveness evaluation were from the subgroup of patients with elevated ALT drawn from the GLOBE study. Poor definition and lack of clarity in the original submission has led to misunderstandings and misgivings on behalf of the ERG, the appraisal committee and the specialist advisors regarding the composition of ALT subgroups and the probity of the analyses. This section seeks to clarify and dispel these misunderstandings	Comments noted. The concerns raised relate to the statistical integrity of the exploratory analysis of subgroups defined by serum ALT levels and their clinical relevance. See FAD section 4.6, 4.7 and 4.11
Novartis (continued)	Patients in the GLOBE study were prospectively stratified at randomisation: firstly according to HBeAg status (positive or negative) and secondly according to serum ALT levels (above or below 2.5 x ULN), in order to ensure even distribution between treatment groups (Table 3). The ALT level used for stratification was based on the serum sample collected at the screening visit (i.e. pre randomisation pre treatment). **Table 3: Stratification of Overall ITT, EE and Safety Populations Based on HBeAg Status and ALT levels – All Randomised Patients** (not reproduced here)	Comments noted.

Consultee	Comments	Response
Novartis (continued)	The submission also presented data for a group of patients identified as the 'interferon eligible' population. This comprised a subset of the HBeAg positive ITT population with screening ALT ≥2 x ULN. Although not initially defined in the study protocol or considered in power calculations, this population was defined in the Statistical Analysis Plan (SAP) prior to database lock and includes all patients in the ITT populations whose ALT value at the screening visit was ≥2.0 x ULN. This subpopulation was to be used to derive analyses of key efficacy parameters that allowed comparisons to historical results from interferon treatment, which typically required patients to have pre-treatment ALT levels ≥2.0 x ULN. This "interferon-eligible" population also corresponds to the patient population recommended for treatment under current APASL guidelines and is consistent with the AASLD guidelines and EASL guidelines (The EASL Jury 2003; Liaw, et al 2005; Lok and McMahon 2007). Although the results for this subgroup were tested for statistical significance (Table 4 below and Table 7 of the MS), it should be noted that these analyses generally lacked adequate power and are not adjusted for multiple comparisons. Therefore, the results of the treatment comparison in this subgroup analysis should be considered exploratory.	Comments noted.
Novartis (continued)	**Table 4: Key efficacy outcomes in ITT/ mITT HBeAg-positive patients with screening ALT ≥2 x ULN - "interferon eligible" population (all at week 104 except histologic response at week 52)** (not reproduced here)	
Novartis (continued)	Uncertainty about the definitions and composition of the ALT subgroup appear to be central to the appraisal committee's reservations about the clinical effectiveness of telbivudine. At several points in the ERG report, concern was raised over apparent discrepancies in the numbers of patients comprising the "interferon eligible" population, whether the subgroup represented 64% or 70% of the total HBeAg positive ITT population, its power to detect treatment differences and its undefined characteristics (ERG report: 3.1.3 p29; 3.1.4 p31; 3.1.5 p32; 3.2 p34; 3.3.1.8 p39; 4.3.1 Tab 6; 4.4.1.2.1 p58, p59; 4.4.1.2.2.p60; 4.4.2 p90; 5.1 p92; 5.2 p93.p94). In the main these uncertainties are easily resolved. The discrepancies in numbers and percentages arise from a misunderstanding of the basis on which the elevated ALT group was defined. For the exploratory efficacy analyses of the "interferon eligible" population, the serum ALT level used to define the group was taken at the Screening visit (up to 6 weeks prior to baseline and randomisation). At the clarification stage, the ERG requested baseline ALT data on the ITT populations, which was supplied. Unfortunately, due to fluctuations in ALT levels, the numbers of patients with ALT above and below 2x ULN differed subtly between screening and baseline visits, thus defining two discrete groups; the former comprising 637/921 (70%) and the latter 588/921 (64%). The ERG appears to have confused the two.	Comments noted. See FAD 4.11.

Consultee	Comments	Response
Novartis (continued)	In Section 4.5 of the ACD, the appraisal committee raised concerns regarding the way the ALT markers were used in terms of both stratification and definition of subgroups for analysis. The report noted that the estimates of efficacy of telbivudine in the ALT > 2 x ULN subgroup were subject to some uncertainty because they were based on post-hoc analyses, and that patients were not stratified according to serum ALT levels. To correct these misunderstandings and reiterate the above, patients were prospectively stratified at the time of randomisation according to screening ALT levels as < or > 2.5 x ULN in order to maintain a balance of patients throughout each treatment arm. The sub-group of patients with ALT >2 x ULN ("interferon eligible" population) was not defined post-hoc but constituted a predefined sub-set of patients proposed for analyses of key efficacy parameters before database lock and analysis (section 9.7.1.1 of the 104 week CSR for NV 02B-007 GLOBE). To summarise, patients were stratified by screening ALT values followed by further subgroup analyses as defined in the statistical analysis plan prior to database lock. The stratification measures effectively balanced the treatment groups for an even distribution of patients for ALT levels in both the ITT and "interferon eligible" populations (Table 3 and 4). While the analyses of ALT subgroups were exploratory and not powered, their inclusion in the MS is of interest and relevance to the decision problem since they demonstrate the superior efficacy of telbivudine over lamivudine in GLOBE patients meeting the treatment threshold for ALT.	Comments noted. See above. The misplaced statement that the GLOBE trial was not stratified according to serum ALT levels has been corrected. See FAD section 4.11.
Novartis (continued)	**5. The HBeAg positive and HBeAg negative cohorts were analysed separately, according to pre-defined criteria and, therefore, neither is influenced by the results of the other.** This section addresses concerns expressed in Section 3.6 of the ACD over the potential for the disparate sizes of the HBeAg subgroups to influence the results of the analysis. The study was designed to demonstrate effects in both HBeAg subpopulations or in the pooled population, if trends in the subpopulations warranted pooling. The primary end point was assessed using a three-step method: First, both HBeAg subpopulations were analysed separately with an alpha-level of 0.04 (95.68% confidence interval). If both subpopulations met the non-inferiority criteria (i.e., if confidence intervals for the treatment difference exceeded –15%), treatments would be compared for superiority within each subpopulation.	Comments noted. Section 3 reports the evidence considered by the Committee including the ERG report.

Consultee	Comments	Response
Novartis (continued)	If superiority was not established within both HBeAg subpopulations, a statistical test for interaction between the treatment group and HBeAg subpopulations was planned, with significance defined at the alpha level of 0.15. If no significant interaction was revealed within each patient subpopulation, a pooled statistical analysis for the overall patient population would be performed using an alpha-level of 0.000933. At the primary analysis (52 week), the therapeutic response and histologic response met the non-inferiority criteria for both HBeAg-positive and HBeAg-negative patients. Within the 3-step procedure, non-inferiority can therefore be claimed for HBeAg-positive and HBeAg-negative patients without performing a pooled analysis. However, the analysis results also showed a stronger treatment effect in HBeAg-positive patients (superiority) than HBeAg-negative (non-inferiority) for both the therapeutic response and histologic response, which showed a statistically significant treatment and HBeAg status interaction [P=0.0315].	Comments noted.
Novartis (continued)	Therefore, because the treatment effects for the HBeAg-positive and HBeAg-negative patients were not similar, both groups were analysed separately (i.e. no pooled analysis was performed), concluding that the two populations were independent of each other. The power calculations presented above (Table 2) were based on assumed enrolment of 700 HBeAg-positive and 500 HBeAg-negative patients and demonstrate that each population was sufficiently 'powered' for the pre-defined efficacy parameters as outlined. Actual recruitment provided 921 HBeAg-positive and 446 HBeAg-negative patients. Since the original power calculations also assumed 7% and 10% drop-out rates at 1 and 2 years and 20% missing histologic data, the actual number of HBeAg-negative patients (n=446) in the primary analysis of the ITT population was close to the original number of 465 used to generate the power calculation (500x93%=465). As a result, the power for the HBeAg-negative group was only minimally affected by the discrepancy between planned and actual patient numbers and provided at least 80% power for all primary and secondary analyses as stated in Table 2. When adjusted for the actual number of patients recruited, the power for the primary endpoint (therapeutic response) for the HBeAg-negative group: At Year-1 88% At Year-2 86%	Comments noted.

Consultee	Comments	Response
Novartis (continued)	Since the therapeutic response rate in the telbivudine group was numerically lower than the lamivudine group at week-52 (75% versus 77% respectively), the results in the HBeAg-negative group would not have differed even if the target number of patients (n=500) had been recruited. This demonstrates that the GLOBE study retained sufficient power to detect differences in the pre-defined efficacy parameters in both HBeAg positive or HBeAg despite their disparate sizes and without mutual interference.	Comments noted.
Novartis (continued)	**6. Both histological *and* biochemical markers are relevant to the treatment decision.** In section 4.4 of the ACD, the relative importance of biochemical and histological markers on the decision to initiate therapy was discussed. The committee was advised that histological evidence of inflammation was the primary indicator for initiation of treatment regardless of ALT levels. Since it reflects on the applicability of GLOBE results to clinical practice, it should be emphasised that **both** ALT **and** liver histology were considered when selecting patients for the study. A liver biopsy compatible with a diagnosis of CHB and ALT level elevated to > 1.3 x ULN at the time of screening were prerequisites for enrolling patients in the GLOBE study.	Comments noted. The Committee was advised by clinical specialists that both histological and biochemical markets are used in diagnosis of chronic hepatitis B. See FAD section 4.3 and 4.4.
Novartis (continued)	Histological response was a pre-defined secondary endpoint and therefore the study was not 'powered' to detect response by changes in ALT level alone. However, because biopsies were only taken at screening and week-52, due to the invasive nature of the procedure, it has been postulated that this endpoint may be too early to detect relevant changes in pathology. It was noted by the ERG that biopsies were not conducted on a more frequent basis due to the invasive nature of the procedure as mentioned above. The ACD correctly points out that ALT levels alone are not an indication for treatment, and that in clinical practice initiation of antiviral treatment usually occurs on the basis of confirmed active liver inflammation and/or fibrosis [via a biopsy], alongside persistently raised serum ALT levels. This practice is also recognised in the licences for all nucleoside/tide analogues, including telbivudine. Consequently, it can be seen that ALT is an important non-invasive marker of liver inflammation and can be used as an indicator of active liver inflammation, where histological evidence is not readily available due to the ethical restrictions within clinical trials. Therefore, ALT provides a clinically relevant indicator of liver inflammation in this patient group and ALT levels raised >2 x ULN has been cited as one of the indications for treatment initiation.	Comments noted.

Consultee	Comments	Response
Novartis (continued)	**<u>Section B: Health Economic Data and indirect comparison</u>** Sections 3.7 to 3.16 of the ACD summarises the comments of the ERG and expert advisors regarding the economic modelling and indirect comparison. Novartis' response to these comments are summarised below and then presented in detail. 1. The viral load model was a genuine attempt to provide a comprehensive representation of a complex disease area. However, we accept that it may have been overly complex given the available data and this was exacerbated by lack of thorough explanation and transparency. 2. We agree with the suggestions of the ERG that the seroconversion model be adapted to reflect more fully the efficacy and resistance of adefovir, and to include entecavir as a comparator. However, when these adaptations to the model were made it was seen that the results changed little. This is in marked contrast to the results calculated by the ERG and we would seek clarification as to why this is the case and to determine which set of results are the most appropriate to use. 3. We accept that two trials (Hou et al and Lao et al) were omitted from the indirect comparison between entecavir and telbivudine. These are now included and results presented. It is noted that the key messages produced by the indirect comparison are now more favourable to Telbivudine than when the Hou et al and Lao et al studies were excluded. We would, however, strongly contest the comments from the ERG that the indirect comparison methods were inappropriate. We would wish the ERG to be more explicit in their criticism in order that we can demonstrate that our methodology was appropriate.	Comments noted.
Novartis (continued)	**1. The viral load model was a genuine attempt to provide a comprehensive representation of a complex disease area. However, we accept that it may have been overly complex given the available data and this was exacerbated by lack of thorough explanation and transparency.** We acknowledge that the ERG has identified a number of deficiencies in the viral load model. We maintain that the viral load approach is a valid one and that our model was constructed with the intention of providing a thorough representation of this complex disease area. However, we concede that, in our attempts to model accurately the disease, the model may have become too detailed for the data which are currently available. That is, although the model encompasses the full spectrum of potential disease states, neither telbivudine nor competitor interventions are able to provide sufficient data with which to populate the model. This situation is most regrettable and we acknowledge that this has provided sufficient uncertainty as to undermine the model in its entirety. Further, by adopting a deterministic approach in simulating the progression of the disease rather than a stochastic one, using data from an unpublished source, this uncertainty has been exacerbated.	Comments noted. See FAD section 4.8 to 4.10.

Consultee	Comments	Response
Novartis (continued)	The use of a non-informative prior was adopted in order to address the lack of data and provide some insight into the effect of same. Given that this is a long-established approach in cases where data is scarce, it is surprising that this has been deemed unacceptable by the ERG. We would appreciate clarification on the measures that the ERG would have preferred to have been undertaken. However, because we have been unable to rectify the problems with the viral load model within the time deadlines for this response, we do not propose to pursue these points further. It is accepted that this will make it difficult to judge the cost-effectiveness of using telbivudine in HBeAg-negative patients.	
Novartis (continued)	**2. We agree with the suggestions of the ERG that the seroconversion model be adapted to reflect more fully the efficacy and resistance of adefovir, and to include entecavir as a comparator. However, when these adaptations to the model were made it was seen that the results changed little. This is in marked contrast to the results calculated by the ERG and we would seek clarification as to why this is the case and to determine which set of results are the most appropriate to use.** In light of the concerns over the viral load model, we would remind the Committee that we also provided a seroconversion model, replicating as far as possible the previous analysis conducted in chronic hepatitis B for TA96. The ERG also raised some concerns with this model and these are considered below.	Comments noted. See FAD sections 4.11, 4.12, and 4.13.

Consultee	Comments	Response
Novartis (continued)	1. Adefovir efficacy as mean of lamivudine and telbivudine (Section 3.13 of the ACD and Section 4.4.1.4.6, p.87). We agree that this underestimated the efficacy of adefovir in that in did not allow adefovir to assume the superior or inferior, position of the three drugs. However, when we followed the ERG's suggested methodology we found that the mean cost per QALY results did not markedly change. It is noted that this approach, whilst better, will also underestimate the uncertainty in adefovir as the alpha and beta within the Beta distribution would be greater than expected. We conducted further analyses halving the alpha and Beta parameters but this did not markedly change the results. Thus, we have not followed the ERG's recommended approach and have, instead, set the efficacy of adefovir to that of telbivudine. The results produced in our reanalysis are provided below (Table 5). It is seen that the results have not markedly changed. Only those strategies containing Adefovir will have results that will change based upon these adaptations. The remaining strategies are provided for reference. **Table 5: Results from the seroconversion model for HBeAg-positive patients- reanalysis including adefovir efficacy equal to telbivudine efficacy** (not reproduced here)	Comments noted. See FAD 4.12 .
Novartis (continued)	2. Use of Locarini et al (2005) resistance data. In our original submission, we had used data from the TA96 appraisal. The ACD (Section 3.13) and the ERG) Section 4.4.1.4.6 p.87) pointed out that a more up-to-date paper was available (Locarini) and we have now incorporated these data into the seroconversion model. It was seen that the data from Locarini were very similar to that used in the original submission. This did not have a marked effect on the data. This is represented in Table 6. **Table 6: Resistance rates from Locarini et al (2005)** (not reproduced here)	

Consultee	Comments	Response
Novartis (continued)	Note that there is ambiguous data in the Locarini paper. In the methods section it is reported that 221 were included, but in the results it claims that 11 out of 217 patients developed resistance. It is the latter figure that we have assumed to be correct. PSA analyses were conducted using the distributions from Locarini and also the recommended approach for the efficacy of adefovir, as detailed in 1 above. These are presented in Table 7. It is seen that the mean results remain very similar, as would be expected given that the 95% CI for the Beta distribution are approximately evenly distributed around the midpoint value. **Table 7: Results from the seroconversion model for HBeAg-positive patients- reanalysis including adefovir efficacy equal to telbivudine efficacy and adefovir resistance as reported in Locarini et al.** (not reproduced here)	
Novartis (continued)	3. Removing patients who progress to decompensated liver disease or liver transplantation. The ERG (Section 4.4.1.1, p58) correctly pointed out that patients in these disease states were allowed to remain under treatment with telbivudine when, in fact, such a course would be outside of the licence. This has been rectified and we assume, instead, that patients developing decompensated disease are treated as though resistance had developed and are switched to an alternative therapy. This also addresses patients requiring liver transplantation since such patients can only reach this state via the decompensated liver disease health state and, therefore, would already have been switched from telbivudine treatment.	

Consultee	Comments	Response
Novartis (continued)	4. No consideration of entecavir. In light of the criticism (ACD, Section 3.13) that we had not included entecavir in our economic modelling, we have replaced lamivudine with entecavir in order that results for the latter could be presented. Time constraints have meant that these data have been entered deterministically. For entecavir we have assumed that the resistance data are as MS for entecavir (0.2, 0.5, 1.2 and 1.2 for years 1 to 4, respectively) and, after year 4, we have assumed no further incremental resistance. We have applied identical seroconversion rates for entecavir as we have for telbivudine, based on the output from our indirect comparison. Both these assumptions are conservative and might favour entecavir. Having incorporated points 1 to 4 above, the resulting comparative ICERs are presented below in Table 8. It is recognised that some of these sequential treatment strategies are not used in practice but we have presented the full results for completeness. **Table 8: Results from the seroconversion model for HBeAg-positive patients- reanalysis including entecavir** (not reproduced here)	Comments noted. See FAD sections 4.11, 4.12 and 4.13.
Novartis (continued)	Despite the changes made to the model itself and the inclusion of entecavir under favourable assumptions, the results are largely unchanged from our original submission. That is, telbivudine followed by best supportive care (BSC) is the most cost-effective option of those considered. It is of some concern that the results differ from those obtained by the ERG and we would appreciate further dialogue to establish which results are correct. A possible explanation is that the data available publicly for use in our analyses and those made available to the ERG differ, thereby accounting for the conflicting results. However, we would request clarification as to the differences observed.	Comments noted. See FAD sections 4.11 and 4.12.

Consultee	Comments	Response
Novartis (continued)	**3. We accept that two trials (Hou et al and Yao et al) were omitted from the indirect comparison between entecavir and telbivudine. These are now included and results presented. It is noted that the key messages produced by the indirect comparison are now more favourable to Telbivudine than when the Hou et al and Lao et al studies were excluded. We would however strongly contest the comments from the ERG that the indirect comparison methods were inappropriate. We would wish the ERG to be more explicit in their criticism in order that we can demonstrate that our methodology was appropriate.** Following the ERG's comments regarding the indirect comparison itself and the fact that it did not include data from the Hou et al (2007) and Yao et al (2007) trials, the analyses have been re-run incorporating these trials. Due to the difficulties in estimating inter-trial variance when there were only two trials for both telbivudine and entecavir, the analyses have been run as a fixed effects model rather than a random effects model, It is commented that this will underestimate the uncertainty within the comparison. The results of this new analysis are presented below, whilst a table of the relative risks used and full details of the output can be found in the Appendix. **Table 9: Indirect comparison of telbivudine and entecavir – Fixed Effects Model:** (not reproduced here)	Comments noted. See FAD sections 4.11, 4.12 and 4.13.
Novartis (continued)	This shows that there is a significant difference in favour of entecavir for HBV undetectability. In addition, non-significant differences are seen in favour of entecavir for ALT Normalisation, and in favour of telbivudine for both seroconversion of e antigen and HBeAg loss. The seroconversion model does not incorporate HBV undetectability (a viral load approach), ALT Normalisation or seroconversion of the e antigen. The seroconversion model does, however, allow for HBeAg loss. Our indirect comparison shows that Telbivudine is likely to be better in promoting HBeAg loss than Entecavir, however as this is not significant we have conservatively assumed that these interventions are comparable and have used the same rate of HBeAg loss for both.	

Consultee	Comments	Response
Novartis (continued)	We would wish to discuss the inappropriateness (or not) of our analyses with the ERG. As the charge of inappropriateness is presently not elaborated upon it is difficult to defend these allegations. It is acknowledged that there was an erroneous comment in the clinical section of the report claiming that indirect comparisons were not valid. However this was referenced to Glenny et al (2005), which does not explicitly cover Bayesian techniques, but does report (p21) that "They require specialist software and a deep statistical understanding, taking them beyond the scope of many research groups". We believe we have this understanding and have conducted the most appropriate analyses, however the author of the erroneous statement was not aware that this work was being undertaken. We would also dispute the accusation that the indirect comparison was visual only (as the statistics are reported). We additionally provided graphical representation of key output in order that the ERG could determine that the analyses undertaken were robust.	Comments noted. See FAD sections 4.11, 412 and 4.13.
Novartis (continued)	**Section C: Review date** We are pleased that the Appraisal Committee has suggested a review date of February 2009, coinciding with the review date for TA96. It is our opinion that the available drugs for the treatment of chronic hepatitis B would be best appraised as a full MTA, rather than the current mixed approach of one MTA and a series of STAs. Moreover, we would suggest that some of the difficulties faced in the appraisals of both telbivudine and entecavir are a direct result of this current approach. This approach has also led to the somewhat perverse situation whereby adefovir and pegasys are recommended for use in HBeAg-negative patients despite their having been independently appraised using a model which could not possibly demonstrate cost-effectiveness in such patients. Consequently, the burden of proof is significantly greater for telbivudine and entecavir (and, presumably, tenofovir if it is also appraised as a STA) than was the case for adefovir and pegasys. At the very least, this must be deemed inconsistent.	Comments noted.
Novartis (continued)	**Summary** In summary, despite the deficiencies in the viral load model, we believe that the clinical data and seroconversion model together provide comprehensive evidence that telbivudine represents a cost-effective use of NHS resources for the treatment of HBeAg-positive patients. The dismissal of the GLOBE data as being of no clinical significance and the discrepancies we have identified between the ERG's results from re-running the seroconversion model and our results are of particular concern. These points must be investigated further.	Comments noted.

Consultee	Comments	Response
British Infection Society	General comments on the STA This STA examines the utility and cost effectiveness of telbivudine 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 data on telbivudine which has been excluded from the appraisal, although the virological evidence regarding resistance has not been presented in any detail.	Comments noted.
British Infection Society (continued)	ii) Telbivudine is, like lamivudine, a nucleoside analogue reverse transcriptase inhibitor of HBV replication. Resistance to telbivudine is mediated by mutations at 181T and 204V/I on the polymerase gene, the same mechanism as lamivudine resistance. Clinical studies have shown a 22% telbivudine resistance rate after 2 years treatment. This was lower than the rate seen for lamivudine in the same trial (although similar to that reported for lamivudine in other trials). However telbivudine resistance is likely to increase in at least a linear fashion year on year. In a disease in which treatment will continue for many years or possibly for life, these levels of resistance are completely unacceptable. Given the availability of drugs with much lower rates of resistance, neither lamivudine nor telbivudine should be used as monotherapy in treatment naive HBV infected patients. In addition any virus which is already resistant to lamivudine is likely to have decreased susceptibility to telbivudine, making the latter unsuitable as second line therapy. iii) Regardless of economic modelling, the pattern of genotypic mutations that is seen in hepatitis B virus exposed to telbivudine (and which confers resistance to the drug, and cross-resistance to other drugs) make it unsuitable as a first line agent for monotherapy in chronic HBV. However it is a potent antiviral drug, and may have a role when given in combination with another agent; this remains to be addressed through further research.	Comments noted. See FAD section 4.5
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 set out in the Appraisal Consultation Document. The RCN will welcome guidance to the NHS on the use of this health technology.	Comments noted.

Consultee	Comments	Response
Royal College of Physicians	i) Do you consider that all of the relevant evidence has been taken into account? The pivotal telbivudine study design improves upon previous evaluations of nucleosides, as the design included a 2 year assessment of efficacy and resistance, after continuous therapy- a situation that realistically approximates current continuous use of nucleoside analogues for most patients. A large number of both HBeAg positive and negative patients were included. These are strengths of the study design. Telbivudine clearly has greater potency than lamivudine in terms of DNA suppression. It is more difficult to discern differences in HBeAg seroconversion rates on treatment between these agents but the two year data indicate that 38% of patients with ALT between 2 and 5 times the ULN lost HBeAg, compared to 29% of lamivudine treated patients. These rates approximate those seen after one year with pegylated interferon. Generally HBeAg loss or seroconversion has not been measurably greater with more potent agents at one year; It may be that an immune response is required to achieve and sustain HBeAg loss in a greater percent of HBeAg positive patients. It is also difficult to quantitate differences in histological outcome between comparator agents at one and two years, given the time required for necroinflammatory and fibrosis repair; however improvements from baseline are noted. It is correct that a subset of patients with raised serum ALT have been analysed in this study but the subset reasonably pertains to a clinically defined group for whom hepatitis treatment is indicated. As pointed out in an earlier submission, and recognised by the Evidence Review Group report, resistance does emerge at a slower rate than lamivudine; however, its rate is clinically significant in patients who do not show a rapid decline in viraemia. This is a disadvantage of telbivudine compared to other more recently tested agents, and will require close DNA monitoring for early salvage in patients who develop resistance. These data require that for patients with high viral loads, further data regarding de novo combination treatment is required. *ERV references: The missing references sited by the ERV were in fact posters and presentation abstracts of the Digestive Disease Week of 2007 not the 108th AASLD meeting (AASLD has held 58 meetings)*	Comments noted. See FAD section 4.3, 4.4, 4.5 and 4.6.

Consultee	Comments	Response
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? 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 serum ALT in large cohorts of Chinese patients and the subsequent risk of cirrhosis and HCC. Whilst incomplete, these date indicate the risk to infected individuals of persistent HBV infection, which may change existing equations for modelling progression. There should be some caution in calibrating these models given the current level of uncertainty of assessing the natural history of hepatitis B in the UK population. The approach used for modelling HBeAg negative and positive disease appears reasonable given the different natural history of these diseases. The time horizons are reasonable. It is noted that 63% of HBeAg positive patient and 57% of HBeAg negative patients in globe study had ALT > 2 ULN; Although this group were not predefined, their inclusion in an analysis mirrors clinical practice and indications for treatment in several guidelines. In the HTA model, resource use estimates that patients were seen 11 times annually; in fact patients given nucleoside analogues are seen at 3-4 monthly intervals i.e. three times per year. We note that for HBeAg positive patients (page 79) telbivudine has a 71% and 49% probability of being cost effective at a willingness to pay threshold of £20,000 for HBeAg positive and negative patients respectively. We also note the data from table 4 (page 81) which I take to imply that neither lamivudine followed by adefovir nor lamivudine has a greater than 50% probability of being cost effective at a threshold willingness to pay of £20,000 per QALY? The ITT analysis should indeed be presented as a modified ITT analysis - 6 patients were randomised and did not receive study drug; however these numbers would not materially affect the results. 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. 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. Adefovir will rapidly lose importance in treatment, relative to tenofovir, given its lack of potency in HBeAg positive patients, the poor primary response observed in 30%, resistance rates after 2 years, as well the relative cost of these agents.	Comments noted. See FAD section 4.7, 4.8, 4.9, 4.10, 4.11, 4.12 and 4.13.

Consultee	Comments	Response
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? The most appropriate place for telbivudine in the pathway of care of hepatitis B remains to be determined, but based on the available evidence, telbivudine could be used more effectively than lamivudine for patients with raised serum aminotransferases (> 2x the ULN) and lower levels of hepatitis B replication, as viral suppression was more effective in this group, and resistance rates were lower. It remains to be determined whether telbivudine would be used as a monotherapy or in combination, but it seems clear that for patients with higher levels of replication (> 10^6 copies/ml) combination therapy, as for lamivudine will become the norm. Lamivudine is effectively 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 positive patients in the UK, and less so for HBeAg negative patients, although so recommended in NICE. This is largely related to patient choice, given the side effect profile of interferon. Pegylated interferon must of course be a consideration for appropriate patients. Telbivudine and entecavir clearly have different resistance profiles, but the indirect visual comparison with entecavir for cost effective analysis is problematic given the differing study designs and measurements. The study design of the entecavir HBeAg positive and negative trials leaves much to be desired and have been repeatedly criticised.	Comments noted. See FAD section 4.12 and 4.13
Royal College of Physicians (continued)	iv) Are there any equality related issues that need special consideration that are not covered in the ACD? NICE approval of telbivudine should lead to clinical guidelines based on evidence that will direct the appropriate use of telbivudine, avoiding resistance. Of relevance, the current NICE guidelines must be questioned, given the current evidence that lamivudine is not considered an optimal first line monotherapy drug for the treatment of hepatitis B. Telbivudine may be suitable for patients with lower levels of HBV replication and where close monitoring for resistance is in place.	Comments noted.

Consultee	Comments	Response
Nominated expert on behalf of the Hepatitis B Foundation UK	➢ The Hepatitis B Foundation UK is very disappointed that NICE is minded not to approve Telbivudine as a treatment for patients with hepatitis B ➢ Telbivudine for the treatment of chronic hepatitis B gives improved treatment options in this area of significant unmet medical need. Clinicians need to be able to have choice in order to treat patients according to their needs ➢ Studies at one year show that Telbivudine has shown greater HBV DNA reductions than Lamivudine, which is known to develop resistance in 80% of patients with in one year. Adefovir also has resistance problems with 3% developing the problem in three years ➢ Without a range of treatments new mutations will develop and patients with resistance will continue to develop cirrhosis and liver cancer ➢ 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 out patient 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 of both surgery and chemotherapy. Determining the value of new drugs for the treatment of hepatitis B drug acquisition must be balanced against expected benefits in morbidity and mortality and cost avoidance from disease progression. ➢ The Foundation feels that bearing in mind some 2800 patients have primary liver cancer in a year and some 700 people need a transplant it is more cost effective to treat than to await the costly and frequently failing treatment for cancer and or cirrhosis ➢ In view of the limitations of current treatment and the problems of expensive second line treatments for cirrhosis, liver cancer and end stage liver disease it would be beneficial to both patients their families and professionals to have a treatment that they could use. This group of patients deserve to have a therapy to meet their unmet needs The Foundation is also concerned that should this therapy not be approved the UK has little else to offer these patients who may have developed resistance and may have high levels of virus. Surely there is a need to consider the very real public health issue of controlling as best as possible and infectious disease	Comments noted. See FAD section 4.3, 4.4, 4.5 and 4.6 Comments noted. See FAD section 4.11, 4.12 and 4.13

Consultee	Comments	Response
Nominated expert on behalf of the British Society of Gastroenterology	**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; telbivudine is more potent than lamivudine and in sequential use pathways would be preferable to lamivudine; - the need for long term, possibly lifelong, therapy and the observed development of drug resistance within the early years of use of telbivudine as a single agent, necessitate that this drug is considered in a management algorithm which includes rescue with adefovir or de novo use of combination telbivudine and adefovir. The evidence base is complete and the ACD summary takes this into account.	Comments noted.
The British Society of Gastroenterology (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?** Yes.	Comments noted.
The British Society of Gastroenterology (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?** Yes at the present time but projecting forward to the stage when tenofovir is available, a drug which is more potent than adefovir , and controls lamivudine and telbivudine resistance variants, we will need to consider whether telbivudine and tenofovir as sequential therapy or de novo combination therapy are more effective in controlling long term resistance than entecavir +/- tenofovir. Thus telbivudine might need to be re-evaluated as an investigational drug in combination with tenofovir in long term studies.	Comments noted. See FAD sections 4.13.

Consultee	Comments	Response
Bury PCT	**i) Do you consider that all of the relevant evidence has been taken into account?** I agree that all of the relevant evidence has been taken 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?** Based on the exceedingly thorough Evidence Review Group Report, the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and therefore the preliminary views on the resource impact and implications for the NHS are appropriate. **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?** The provisional recommendation of the Appraisal Committee is sound and is a suitable basis for the preparation of guidance to the NHS. **iv) Are there any equality related issues that need special consideration that are not covered in the ACD?** No.	Comments noted
South Asian Health Foundation	I was recently sent the appraisal consultation document for telbivudine in chronic hepatitis B infection. This was in my role within the South Asian Health Foundation (UK). I just wanted to let you know that I have reviewed the document and on behalf of the Foundation I do not have any comments to add. I am in broad agreement with the conclusions of the Committee.	Comments noted
Department of Health	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. 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

Comments from commentator organisations

Consultee	Comments	Response
Southampton Health Technology Assessments Centre (SHTAC)	Clinical effectiveness 1. There is only one small error - in section 3.2, p.5 of the ACD, it states there were 1397 patients in the Globe study. This should be 1367.	Comments noted. Amended in FAD
SHTAC (continued)	Cost effectiveness 2. Section 3.7 (p 8) of the document states "No comparisons were made in the seroconversion model of telbivudine against adefovir dipivoxil or lamivudine as separate treatments." - not strictly true. The MS did not present any comparisons of telbivudine against other agents (all comparisons were, incorrectly, made against best supportive care). However such comparisons could be made (and were done by the ERG, see Table 5 of the ERG report, column 5 headed "compared with next best strategy"). The current wording suggests that the MS did not model lamivudine as monotherapy, which is not correct.	The wording has been amended for the FAD
SHTAC (continued)	3. Section 3.9 (p 8) of the document states "Following the identification of errors in the manufacturer's original economic model by the ERG, amended base-case analyses were presented." - this should probably be clearer that the errors were only in the viral load model and results were only re-submitted for the viral load model.	The wording has been amended for the FAD
SHTAC (continued)	4. Section 3.11 (p 9) of the document reports the ICERs from the seroconversion model using the comparisons reported by the manufacturer only - i.e. the incorrect analysis comparing all strategies against best supportive care. You may want to mention that the ERG conducted an analyses where options were eliminated using dominance/ extended dominance. This gives an ICER of £24,277 for telbivudine followed by adefovir when compared with telbivudine (rather than £15,684, as reported in MS (and ACD), for telbivudine followed by adefovir when compared with best supportive care).	Comment noted
SHTAC (continued)	5. Section 3.14 (p 11) of the document states "The ERG noted discrepancies in the calibration factors in the risk equations used for the compensated cirrhosis and hepatocellular carcinoma states in the original and resubmitted economic models and those listed in the appendices to the manufacturer's submission" - it should be clearer that this only applies to the viral load model.	The wording has been amended for the FAD (3.15)
SHTAC (continued)	6. Section 3.14 (p 11) of the document states "In general, the ERG noted that the manufacturer's submission did not provide summaries of the model parameters, " - this is not strictly true. The main body of the MS did not contain details of model parameters. However the parameters were documented in appendices to the MS.	The wording has been amended for the FAD

Consultee	Comments	Response
SHTAC (continued)	7. Section 3.15 (p 12) of the document states "The cumulative effects of varying these parameters gave an ICER of £8,400 per additional QALY gained." - it should be stated that this ICER was calculated for telbivudine followed by adefovir compared with lamivudine followed by adefovir.	The wording has been amended for the FAD (3.17)
SHTAC (continued)	8. Section 3.16 (p 12) of the document states "The ERG conducted a PSA using the viral load model with a 'non-informative prior' of 0.0 only; replacing constant health state utilities with non-constant age-specific utilities and applying model calibration factors for risk of advanced liver disease." - it should be clearer what calibration factors were used. We replaced the values in the electronic model with those reported in appendix C of the manufacturer's submission.	The wording has been amended for the FAD (3.18)
SHTAC (continued)	9. Section 3.16 (p 12) of the document states "The ERG also conducted a PSA using the seroconversion model; the results differed from the manufacturer's analysis in that over a cost effectiveness threshold of £20,000 to £25,000 per additional QALY, the optimal strategy in the ERG's analysis was lamivudine followed by adefovir whilst telbivudine was the optimal strategy in the manufacturer's PSA." - the range of WTP over which lamivudine followed by adefovir was optimal, as stated in the ERG report, was £22,000 to £24,000. You may also want to state that the strategy of telbivudine followed by adefovir remained the optimal strategy at higher values of WTP (i.e. over £25,000).	The wording has been amended for the FAD (3.18)
SHTAC (continued)	10. Section 4.5 (p 15) of the document states "The Committee was advised by the clinical specialists that estimates of the efficacy of telbivudine in this subgroup were subject to some uncertainty because they were based on a post-hoc analysis, and randomisation was not stratified according to serum ALT levels." - this is not strictly correct. Randomisation was stratified by ALT, but not at 2 X ULN. According to the MS randomisation (section 5.3.1, page 29) "Treatment assignments were stratified by HBeAg status (positive or negative) and by serum ALT level (above or below 2.5 times the upper limit of normal)."	Comment noted.