NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Tenofovir disoproxil fumerate 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
Hepatitis B foundation	We are delighted with the Appraisal Committee's preliminary recommendations. Hopefully the end result will be a positive Final Appraisal Determination and the publishing of final guidance. This technology is a very important new treatment option for chronic hepatitis B and the sooner it is freely available on the NHS the better it will be for patients.	Comment noted
Hepatitis B foundation (cont)	*Do you consider that all of the relevant evidence has been taken into account?* Yes, the Appraisal Committee has taken into account the evidence from clinicians and patient experts, as well as data available on the clinical and cost effectiveness of the technology.	Comment noted
Hepatitis B foundation (cont)	*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, summaries are reasonable interpretations and preliminary views are appropriate.	Comment noted
Hepatitis B foundation (cont)	*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?* Most definitely, yes.	Comment noted

Consultee	Comment	Response
Hepatitis B foundation (cont)	*Are there any equality related issues that need special consideration that are not covered in the ACD?* No.	Comment noted
South Asian Health Foundation	On behalf of SAHF I have no comments to make and endorse / support the recommendations proposed for tenofovir in the management of chronic hepatitis B	Comment noted
College of Pathologists and the UK Clinical Virology Network	I write on behalf of the College of Pathologists and the UK Clinical Virology Network. This is a safe drug that is well known to virologists and those who treat HIV as well as, increasingly, those who treat HBV. It is clear it is already becoming frontline because of its efficacy and perceived low level of resistance. Your recommendations endorse this view. We have no substantive problems with it. I have insufficient knowledge of economic models to comment on those aspects.	Comment noted
College of Pathologists and the UK Clinical Virology Network (Cont)	I would have thought NICE should not become embroiled in discussions regarding single use tenofovir or its use in combination. This area is at an early stage (and confused, with little evidence either way) for all drugs used in HBV therapy and whatever NICE's recommendations, it will be used according to upcoming clinical trial data as hepatologists are a large international community and mostly do what everyone else is doing ie whatever has been shown in trials to work. Just because combination therapy is used in HIV does not mean it should be used in HBV.	Comment noted. See FAD 4.7

Consultee	Comment	Response
The Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Tenofovir disoproxil fumarate for the treatment of hepatitis B. Nurses working in this area of health have reviewed the ACD for this appraisal and do no have any other comment to add. The RCN will welcome guidance to the NHS on the use of this health technology	Comment noted.
Gilead	*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?* Gilead fully supports the Appraisal Committee's preliminary recommendation that tenofovir be used within it marketing authorisation and we acknowledge that the current body of evidence supports first line use of tenofovir as monotherapy.	Comment noted

Consultee	Comment	Response
Gilead (continued)	However, we request the removal of "used as monotherapy" as this wording does not appear in our marketing authorisation[1] and could therefore be perceived as a restricted recommendation. As discussed at the public hearing the EASL guidelines recommend tenofovir and entecavir as the preferred first line NUCs.[2] The EASL guidelines clearly state there are circumstances where combination therapy be used: "In case of resistance, an appropriate rescue therapy should be initiated with the most effective antiviral effect and the minimal risk to induce multiple drug-resistant strains. • Lamivudine resistance: add tenofovir (add adefovir if tenofovir not yet available). • Adefovir resistance: it is recommended to switch to tenofovir if available and add a second drug without crossresistance. If an N236T substitution is present, add lamivudine, entecavir or telbivudine or switch to tenofovir plus emtricitabine (in one tablet). If an A181T/V substitution is present, add entecavir (the safety of the tenofovir–entecavir combination is unknown) or switch to tenofovir plus emtricitabine. • Telbivudine resistance: add tenofovir (add adefovir if tenofovir not yet available). The long-term safety of these combinations is unknown. • Entecavir resistance: Add tenofovir (the safety of this combination is unknown). • Tenofovir resistance: resistance to tenofovir has not been described so far. It is recommended that genotyping and phenotyping be done by an expert laboratory to determine the cross-resistance profile. Entecavir, telbivudine, lamivudine or emtricitabine could be added (the safety of these combinations is unknown)."	Comment noted. The guidance has been amended for the FAD. See also FAD section 4.7

Consultee	Comment	Response
Gilead (continued)	If the wording of the NICE guidance is interpreted as an absolute restriction to the use of tenofovir combination therapy this would be contrary to EASL guidelines and good clinical practice.	See FAD section 4.7 Also EASL guidelines say: "There are as yet no data to indicate an advantage of *de novo* combination treatment with NUCs in naïve patients receiving either entecavir or tenofovir" (page 8).
Gilead (continued)	Finally, it should be noted that NICE did not explicitly state entecavir only be "used as monotherapy". Inclusion of the monotherapy wording for tenofovir could be perceived as a restriction and would be inconsistent with previous NICE guidance for a drug with an identical licence indication.[3]	The Committee discussed the relevance of previous NICE guidance on chronic hepatitis B and where in the treatment pathway tenofovir disoproxil should be considered

Consultee	Comment	Response
Gilead (continued)	***Section 3.3:*** *The manufacturer's submission presented evidence on the clinical effectiveness of tenofovir disoproxil from two randomised controlled trials (RCTs) that compared tenofovir disoproxil with adefovir dipivoxil.* ***The protocol for both studies specified that the populations would be people who had not previously received nucleotide analogue therapy.*** The protocol for our pivotal HBeAg negative study allowed recruitment of patients with prior experience of lamivudine or emtricitabine.[4] 17% of patients who received tenofovir from baseline and 18% of patients who received adefovir for the first 48 weeks had previous treatment experience with lamivudine or emtricitabine.[4] Tenofovir produced a similar HBV DNA response in patients who had previously received lamivudine and in those who had not. "An evaluation of the treatment response in subgroups defined by baseline characteristics showed no significant interactions at the alpha level. Among patients treated with tenofovir, 90% of patients who had received lamivudine versus 88% of those who had not received lamivudine had HBV DNA suppression to less than 400 copies per millilitre".[4] Please note that the findings of 102 and 103 have now been published in the New England Journal of Medicine.[4]	Comment noted. Section 3.3 of the FAD has been amended accordingly

Consultee	Comment	Response
Gilead (continued)	**Section 3.6:** *The incidence of severe, life-threatening or disabling adverse events was similar between treatment groups, with no deaths reported in either study.* ***However, statistically significantly more participants had at least one treatment-related adverse event in the tenofovir disoproxil treatment group in one study (p = 0.018)****. The incidence of arthralgia was statistically significantly higher for the group receiving tenofovir disoproxil in the other study (p = 0.003).* As discussed in our submission and the ERG report please qualify that the "statistically significantly" difference was due to "mild nausea". The Marcellin NEJM 2008 publication states: "The safety profiles observed in both studies (102 & 103) were consistent with the known safety profiles for tenofovir in patients with HIV infection and for the safety profiles for adefovir dipivoxil in patients with HBV infection. Nausea was the only adverse event that consistently occurred more frequently in the group of patients who received tenofovir than in the group of patients who received adefovir dipivoxil (9% vs. 3%). Among the cases of nausea that were considered to be related to tenofovir, nausea was mild except for one case of grade 2 (moderate) nausea." [4]	Comment noted. Section 3.6 of the FAD has been amended accordingly.

Consultee	Comment	Response
Gilead (continued)	**Section 4.4:** *The Committee expressed concern that the results for tenofovir disoproxil in the indirect mixed-treatment comparison were not similar to those in individual RCTs, but this would be expected given that tenofovir disoproxil was linked by only one comparator.* We would like to provide the following clarification regarding this misunderstanding: The absolute estimate figures have been confused with the relative difference figures, which had the impact of exaggerating the difference: a 90% absolute estimate from the meta-analysis was contrasted with a 20-fold relative difference observed in the trial. The meta-analysis actually suggests that around 94% of patients receiving tenofovir will achieve undetectable HBV DNA and that the odds of responding to tenofovir are 27 times as high as those of responding to adefovir (vs. a 20-fold difference observed in study 103). The absolute probability of responding to treatment differed from those observed in clinical trials because the probability of viral suppression with tenofovir was calculated from the log-odds ratio (OR) for tenofovir relative to lamivudine (and the odds of responding to lamivudine) rather than being based on the absolute proportion of patients who achieved undetectable HBV DNA with tenofovir. This was conducted because analyses on relative treatment effects have been shown to be more robust and much less prone to bias than those based on absolute outcomes in individual trials; subsequently, it is generally recommended that indirect comparisons should be based on the log-OR rather than the absolute outcomes observed in each trial Although the mean odds ratio for response with tenofovir relative to adefovir that was calculated in the MTC (26.93) is higher than the odds ratio observed in study 103 (20.3), comparisons of relative efficacy should in fact be based on the log-odds ratios (on which the MTC was based), which are extremely similar between the MTC (log-OR for tenofovir vs adefovir=3.051) and study 103 (log-OR for tenofovir vs adefovir=3.010). It is appropriate to compare measures of relative effect based on the log-OR rather than ORs because the MTC was based on log-ORs and because the exponent of the mean log-odds ratio is not equal to the mean odds ratio. We attach data on the log-OR and OR output from the MTC.	The log-ORs presented (3.051 and 3.010) were not reported in the original manufacturer's submission. Also see section 4.4 of the FAD "The Committee noted discrepancies between the results from the mixed-treatment comparison and those from the individual RCTs. The Committee also took into account the ERG's remarks on the quality of the analysis of the mixed-treatment comparison. However the Committee agreed that the identified weaknesses in the analysis were not sufficiently serious to prevent it making a decision on the use of tenofovir disoproxil in chronic hepatitis B in the light of the evidence available from the individual RCTs"

Consultee	Comment	Response
Gilead (continued)	**References** 1. Viread Summary of Product Characteristics 2. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. Journal of Hepatology 50 (2009) 227–242 3. Baraclude Summary of Product Characteristics 4. Patrick Marcellin, M.D., E. Jenny Heathcote, M.D., Maria Buti, M.D et al. Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B. N Eng J Med 2008; 359: 2442-2455,	Noted.

Comments from commentator organisations

Commentator	Comment	Response
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted
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
Mark Nelson	I feel that it is a well written and accurate report	Comment noted
Mark Nelson (cont)	1. There is a suggestion that tenofovir should be used as an option only post interferon or when interferon is contraindicated. I think the wording could be improved as really many physicians would choose antiviral therapy ahead of interferon in nmany if not the majority of patients and there are specific patient groups where interferon may be considered eg. high ALT low viral load	Comment noted. The FAD only issues guidance in relation to tenofovir disoproxil. The evidence submitted did not include a comparison with interferons as first line therapy.

Commentator	Comment	Response
Mark Nelson (cont)	2 I would prefer a more positive approach to the possibility of dual therapy eg saying could be considered in those at risk of developing resistance eg v high viral load although I agree evidence of anyone developing tenofovir resistance is lacking	Comment noted. See FAD section 4.7
Mark Nelson (cont)	3 A mention of the necessity to have been tested for hiv	Comment noted. Section 1 of the FAD states that his guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.
Mark Nelson (cont)	4 Mention of the need for renal monitoring	Comment noted. The guidance states that tenofovir disoproxil is recommended within its marketing authorisation. The SPC for tenofovir states that renal function should be closely monitored in patients with renal insufficiency.
Bristol-Myers Squibb	Bristol-Myers Squibb (BMS) supports the availability of new therapies such as tenofovir (TDF) in the UK for the treatment of chronic hepatitis B (CHB). However, BMS feels that some of the statements and interpretations of the clinical and cost effectiveness information in the Appraisal Consultation Document (ACD) for TDF are not reflective of the data and may mislead clinicians and decision-makers in the UK. In addition the appraisal committee themselves have expressed concern about the network meta-analysis undertaken by the manufacturer used to estimate the clinical efficacy for TDF. BMS believes therefore, that it is an unsound on which to make recommendations about TDF in CHB patients. BMS would like to elaborate on three key areas of concern:	Comment noted.

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	1) At the core of the clinical and cost effectiveness evidence base for TDF is a network meta-analysis that has some major limitations which BMS believes render it an unsound basis for clinical evidence based decision-making. BMS would therefore, request that statements within the ACD concerning the superior efficacy of TDF versus entecavir (ETV) in HBeAg positive patients (section 3.7) be amended to reflect that the manufacturer's analysis of undetectable HBV DNA did not correct for differences between studies in baseline viral load. Indeed, it should be stated in the ACD that a similar percentage of patients achieve undetectable DNA at year 1 with ETV compared with TDF (section 4.4). Furthermore, a network meta-analysis examining the clinical effectiveness of TDF in HBeAg negative patients was not possible due to lack of data connecting TDF to the evidence network. BMS also request that the ACD is amended to reflect that the clinical effectiveness of TDF in HBeAg negative patients has not been established.	Comments noted. The clinical effectiveness of tenofovir disoproxil in HBeAg negative patients has been established, via the 102 RCT. Section 3.7 of the FAD states "For HBeAg-positive nucleoside-naïve participants, **the mixed-treatment comparison showed** that tenofovir disoproxil had a statistically significantly higher predicted probability of HBV DNA suppression than all comparators" The Committee was aware that the estimates of effectiveness relative to other treatments derived from the mixed treatment comparison is uncertain. See FAD section 3.14 and 4.4.

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	2) BMS believes that the ACD is misleading in that it states that TDF has an equivalent or better resistance profile compared to other CHB therapies including ETV at 1 year (section 4.6). BMS would suggest that the ACD clarifies that TDF is equivalent to ETV at 1 year for naïve patients only, and highlights that the TDF trial design does not allow evaluation of TDF resistance beyond 72 weeks.	Comment noted .Section 4.6 of the FAD states ".The Committee agreed that tenofovir disoproxil had a similar or more favourable resistance profile at 1 year compared with other available treatments for chronic hepatitis B. However, the Committee agreed that given the data available it could not be assumed that this low rate of resistance would be maintained in the long term.
Bristol-Myers Squibb (cont)	3) The ACD relies upon cost effectiveness estimates (section 4.5) for TDF that may be under-estimated because they are based upon biased clinical efficacy estimates from the network meta-analysis and TDF resistance data. BMS request that the ACD highlights that the cost per QALY for TDF is likely to be higher than that stated. In addition, cost effectiveness estimates for the HBeAg negative patient population are based on a network meta-analysis of TDF data for both HBeAg positive and negative rather than HBeAg negatives alone. BMS believe that the resulting cost per QALYs are unreliable and are not representative of the cost effectiveness of TDF in this population. BMS would therefore request that statements within the ACD be amended to reflect that there is insufficient evidence to conclude that 1st line use of TDF monotherapy is the most cost-effective antiviral strategy for managing both HBeAg positive and negative CHB.	Comment noted.

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	More detail is provided on these issues below. **Network meta-analysis** It is important that the ACD is based on a robust summary of the clinical data available and in the absence of head-to-head trials containing all interventions relevant to this appraisal, the use of a network meta-analysis is both inevitable and appropriate. However, while the approach used by the manufacturer is generally acceptable, BMS has major concerns about the validity of the network meta-analysis, and, that the results are not a fair representation of the TDF and ETV efficacy data. Moreover, the manufacturer only performed the network meta-analysis of efficacy for TDF in HBeAg positive patients, and not HBeAg negative patients. BMS would suggest that this is a significant limitation of the evidence base; especially given the vast majority of patients in the UK are HBeAg negative.	Comment noted. The Committee was aware of the limitations of the mixed treatment comparison (see FAD sections 4.4, 4.5 and 4.6)
Bristol-Myers Squibb (cont)	Irrespectively, BMS feels that the network meta-analysis of HBeAg positive patients performed by the manufacturer results in an overstatement of TDF efficacy and an understatement of ETV efficacy. This is highlighted by significant discrepancies between the results of the network meta-analysis and the results from individual trials (as also noted by the appraisal committee in the ACD (section 4.4)). For example, the estimated percentage of TDF-treated HBeAg positive patients with undetectable HBV DNA (<300 copies/mL) using the network meta-analysis is 93.7% (see Table 16 of the manufacturer's submission) whereas the 103 TDF trial with HBeAg positive patients reports 74% (see p50 of the manufacturer's submission).	Comment noted

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	BMS feels that two important drivers of this discrepancy are [i] the fact that the network meta-analysis uses only a single study to link TDF to the rest of the evidence network (and therefore does not consider a more representative selection of the data available), and [ii] the network meta-analysis compares TDF trial 103 with ETV trials 022/ 079 which provides a bias towards TDF as patients in the ETV trials were much more difficult to treat. More specifically, these patients had much higher baseline levels of HBV DNA (up to 1.5 mean log higher; see table below). As a result it is less likely that ETV-treated patients would achieve the end point of HBV DNA less than 300 copies/ml at 48 weeks. Hence, BMS are concerned that this has understated the efficacy of ETV. An alternative way to compare the efficacy of ETV and TDF drugs when baseline HBV DNA levels are different is to compare absolute log drop in HBV DNA from baseline. As the table below shows, ETV has the largest mean reduction in HBV DNA (trials 022 and 079) compared with TDF in the 103 study. However, this would also be subject to the same bias of different baseline HBV DNA levels..	Comment noted
Bristol-Myers Squibb (cont)	Table [not reproduced here]	Comment noted

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	In summary, BMS believes the efficacy estimates from the network meta-analysis are unreliable and statements within the ACD concerning the superior efficacy of TDF versus entecavir (ETV) in HBeAg positive patients (section 3.7) be amended to reflect that the manufacturer's analysis of undetectable HBV DNA did not correct for differences between studies in baseline viral load. Indeed, it should be stated in the ACD that a similar percentage of patients achieve undetectable DNA at year 1 with ETV compared with TDF. This is consistent with the opinion of international experts who do not consider TDF to have superior efficacy versus ETV.i This is also consistent with a real-life retrospective multi-centre cohort study of 199 nucleos(t)ide naive patients treated with 0.5 mg ETV, which showed a 89% cumulative probability of virological response (patients with undetectable HBV DNA <12 IU/mL) at 48-weeks and that response varies depending on baseline DNA. Therefore, inferring comparative efficacy without adjusting for baseline viral load may lead to underestimating the efficacy of ETV.	Comment noted
Bristol-Myers Squibb (cont)	**Resistance** CHB is a long term chronic condition, in many cases requiring continuous therapy, and therefore it is important to consider both the short-term and the long-term resistance profiles of CHB therapies. In particular comparisons between TDF and ETV in nucleos(t)ide naïve CHB patients are difficult to make because there are differences in the trial designs used to collect resistance data for each drug and the number of years for which data is available	Comment noted

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	With respect to short-term data in naïve patients, 0.2% of patients treated with ETV developed resistance at year 1 (representing only one patient out of 663 who developed resistance) versus the 102 and 103 studies for TDF showed that no patients developed resistance out of a total population of 426. These percentages can be considered similar and based on a small difference in the numbers of patients developing resistance it is not possible to conclude that TDF is superior to ETV at one year.	In the context of the economic model, the difference in the proportion of treatment-naïve patients assumed to develop resistance is unlikely to have a substantial impact – since the estimated resistance rates are very low for both entecavir and tenofovir (0.36% vs 0.23% for the first and second year of treatment with each agent, respectively).
Bristol-Myers Squibb (cont)	Moreover, BMS does not believe that the manufacturer can make any comparisons about TDF resistance beyond 72 weeks based on the TDF data set and that therefore the resistance profile for TDF beyond 72 weeks remains unproven (even though 96 week data have been reported). In the 102 and 103 TDF trials, the patients most likely to develop resistance (those with detectable replicating virus above 400 copies per ml) had their therapy intensified with emtricitabine (not licensed, and unproven, for the treatment of CHB) at 72 weeks of therapy to prevent the development of resistance to TDF. This accounted for 15 HBeAg-positive patients in the 103 study (9%) and 2 HBeAg-negative patients in the 102 study (1%). Thus by including the patients who had their therapy intensified, the rate of resistance for TDF may have been under-estimated.	Comment noted

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	In contrast, in the ETV trials, patients were extensively monitored for resistance to ETV, including those most at risk from resistance (patients remaining on ETV monotherapy even if their HBV DNA was detectable during treatment). Five year data for ETV in naïve patients shows a 1.2% rate of genotypic resistance based on a comprehensive analysis of all patients enrolled into the naïve ETV registration trials (see table below; as taken from the Summary of Product Characteristics (SPC) for ETV). The low rate of genotypic resistance seen with ETV over 5 years is most likely due to the potency of viral suppression combined with a high genetic barrier (defined as the need for multiple mutations in order for resistance to occur). The 6 year ETV resistance data will be presented at the forthcoming EASL congress in April 2009.	Comment noted
Bristol-Myers Squibb (cont)	Table: Emerging Genotypic Entecavir Resistance Through Year 5, Nucleoside-Naive Studies [not reproduced here]	Noted

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	The ACD states that the results of the pooled resistance data presented by the manufacturer suggests "…a lower risk of viral resistance over 5 years with tenofovir disoproxil than with adefovir dipivoxil, lamivudine and entecavir in both treatment-naïve and lamivudine-refractory patients." (section 3.9). However as a result of the intensification strategy employed in the TDF trials, and the fact that the nature or number of mutations needed for resistance to TDF to occur have not yet been defined, BMS believes it is inappropriate to extrapolate one year TDF resistance data to the long term. It is therefore premature to conclude that TDF has a superior or even an equivalent resistance profile to ETV in naïve patients. BMS also believes this statement to be inconsistent with international recommendations for treatment-naïve patients. For example, the EASL 2009 guidelines recommend both TDF and ETV as drugs with the optimal resistance profiles. As a result of the above, BMS would strongly suggest all references to TDF having a superior resistance profile to ETV in naïve patients be removed, and clarify that only comparisons up to one year are possible.	Comment noted. The committee were aware of the limitations of the resistance data submitted. (see FAD section 4.6 and ERG report pages 65 to 68)

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	**Cost-Effectiveness of tenofovir** BMS believes the cost effectiveness estimates for TDF stated in the ACD are over-estimated due to biased inputs. More specifically, the clinical efficacy estimates from the network meta-analysis and the resistance data for TDF are two key drivers in the economic model, and are biased estimates of the clinical effectiveness of TDF, as discussed in sections 2 and 3 of this response. As a result the efficacy of TDF in the economic model is likely to be over-estimated and therefore the incremental cost per Quality Adjusted Life Year (QALY) gained is likely to be under-estimated. In addition to this the manufacturer based their cost effectiveness estimates for HBeAg negative patients on the results of a network meta-analysis based on clinical data for both HBeAg positive and negative patients. BMS believes these cost effectiveness estimates are therefore unreliable as they do not capture important differences between the two populations in factors such as duration of therapy. In addition, HBeAg positive and HBeAg negative CHB are well established as being distinct disease entities and HBeAg status is both an effect modifier and an independent predictor of outcomes. Furthermore, the manufacturer focused on virological response (HBV-DNA) and HBeAg seroconverson and did not meta-analyse information relating to either biochemical response (ALT levels) or histological improvement.	Comment noted. The committee were aware of the limitations of the mixed treatment comparison (see FAD sections 4.4, 4.5 and 4.6)
Bristol-Myers Squibb (cont)	BMS would recommend that as a result of such limitations that the ACD highlights that the cost effectiveness results should be interpreted with caution and that the cost per QALY gained for tenfovir is likely to be higher than that estimated by the manufacturer. More details on these and other issues are given below	See FAD 4.5

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	**Clinical efficacy** The results of the network meta-analysis are directly incorporated into the model on sheet 'Efficacy' (E6:N18), thus the potential bias discussed in the network meta-analysis is incorporated into all model outputs. The values from year one are extrapolated to year two and beyond using proportions derived from information in key trials. Thus, if the initial probability is too high then all subsequent values are also too high. As an example of the impact of parameter inflation: The utilities for Active CHB, Viral suppression and HBeAg seroconversion are 0.77, 0.77 and 0.86 respectively. Similarly, the annual probabilities of hepatocellular carcinoma from each of the three health states are 0.48%, 0.11% and 0.50% respectively (utility 0.36). Therefore, for individuals in the active CHB state, increasing the rates of either HBeAg seroconversion or viral suppression leads to: Increased chance of entering a higher utility state Decreased chance of entering a lower utility state Thus, parameter inflation leads to an increase in incremental QALYs. The importance of the results from the network meta-analysis on the economic evaluation is shown in figures 16 and 17 of the manufacturer's submission (p155/156). The key driver of cost-effectiveness was the probability of TDF HBeAg seroconversion with the value used in the model being the output from the NMA.	Comment noted. The committee were made aware of this issue (see ERG report page 67)
Bristol-Myers Squibb (cont)	In addition to this, as stated above, the values used in the model for year two onwards are assumed to be a proportion of year one values (HBeAg seroconversion 95.24%, virological response 62.98%). The model states that these values were derived from six key clinical trials. However, these studies are not identified in either the report or the model and the method used to calculate these values is also not explained. Therefore, BMS has no way to check the calculations and the values should be viewed with caution.	See above response.

Commentator	Comment	Response
Bristol-Myers Squibb (cont)	**Proportion of cirrhotic patients at baseline** All patients are assumed to be nucleos(t)ide naïve at the start of the model and are distributed across the health states on the basis of data on patients attending a single hepatology clinic in London. Of particular interest is the assumption that 5.3% will enter the model in the cirrhotic health state. In response to comments made in the ETV ACD, BMS undertook an additional scenario analysis whereby the proportion of patients starting in the cirrhosis health state was assumed to be 0%, 10% and 20%. As the value increased, the cost-effectiveness of ETV decreased. The rationale behind the values used was that they are likely to be those that present in the general population and were the values used by the ERG in their sensitivity analysis. Assuming that the same relationship holds for TDF, then a scenario analysis would need to be performed to assess the impact of different starting distributions on the corresponding incremental cost per QALYs. On the basis of information presented in table 45 (p158) such an analysis has not been carried out by the manufacturer.	Comment noted.
Roche	WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT Roche believe that all relevant evidence has been taken into account.	Comment noted.

Commentator	Comment	Response
Roche	WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE Roche believe that the evidence given by the manufacturer have been generally interpreted satisfactorily by the ERG and the Appraisal Committee. Roche is concerned about the basis of the conclusions drawn about the HBeAg-negative subgroup of patients. The manufacturer points out that there can be no meaningful analysis due to lack of data but presents an analysis combining HBeAg-negative and HBeAg-positive and using the HBeAg-negative results as a covariate. Inferring clinical results based on this analysis may lead to an overestimation or underestimation of the results. In turn this may impact the cost-effectiveness of tenofovir disoproxil in this subgroup.	Comment noted. See FAD section 4.5
Roche	WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS Roche believe that the provisional recommendations are sound.	Comment noted.

Web comments - None received