Response to the Appraisal Consultation Document for tenofovir	
Confidential information is highlighted and underlined, e.g. tenofovir	
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1. Summary

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:

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.

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.

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.

More detail is provided on these issues below.

2. 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.

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).

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.[1] 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.

Registrational Study	**Study 103**		**BMS 022**		**BMS 079**	
Therapeutic	***Tenofovir***	***Adefovir***	***Entecavir***	***Lamividine***	***Entecavir***	***Adefovir***
Number of patients	176	90	354	355	33	32
Mean baseline HBV DNA	8.6	8.88	9.62	9.69	10.2	9.88
HBV DNA <400 copies/ml	78 (ITT)	13 (ITT)	-	-	-	-
HBV DNA <300 copies/ml	74%	12%	67%	36%	58%	19%
Mean HBV DNA reduction	-6.17	-3.93	-6.9	-5.4	-7.28	-5.08

Note: ITT – Intention to Treat

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.[2] 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[3] 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.

3. 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.

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[4,5]) 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.

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).[6] 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.

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.

Table: Emerging Genotypic Entecavir Resistance Through Year 5, Nucleoside-Naive Studies[7]

	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	663	278	149	121	108
Patients in specific year with:					
- emerging genotypic ETVr[c]	1	1	1	0	0
- genotypic ETVr[c] with virologic breakthrough[d]	1	0	1	0	0
Cumulative probability of:					
- emerging genotypic ETVr[c]	0.2%	0.5%	1.2%	1.2%	1.2%
- genotypic ETVr[c] with virologic breakthrough[d]	0.2%	0.2%	0.8%	0.8%	0.8%

[a] Results reflect use of a 1-mg dose of ETV for 147 of 149 patients in Year 3 and all patients in Years 4 and 5 and of combination ETV-LAM therapy (followed by long-term ETV therapy) for a median of 20 weeks for 130 of 149 patients in Year 3 and for 1 week for 1 of 121 patients in Year 4 in a rollover study.

[b] Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).

[c] Patients also have LVDr substitutions.

[d] $\geq$ 1 $\log_{10}$ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

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.

4. 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.

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.

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.

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.

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.[8.]

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.

References

[1] Poynard et al. Sustained viral response is dependent on baseline characteristics in the re-treatment of previous Interferon/Ribavirin non-responders: Final results from the EPIC program. European Association for the Study of the Liver. 2008

[2] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B . J Hepatol 2009; 50(2): 227-242.

[3] Lampertico P, et al. 59th AASLD Meeting, October 31-November 4, 2008, San Francisco, USA. Poster 869. *(Hepatology,* 2008;48(4, suppl 1):722A.).

[4] Extracts from Bristol-Myers Squibb. Scientific Report: Entecavir – Year Four Resistance Summary Report. BMS, 2007

[5] Colonno RJ., Rose RE., Pokornowski K., Baldick CT., EffersD., Yu A. et al. four-year assessment of entecavir resistance in nucleoside-naïve and lamivudine-refractory patients (abstract) J Hepatol 2007; 46(suppl 1) S294

[6] Snow-Lampart et al., 59th AASLD Meeting, October 31-November 4, 2008, San Francisco, USA (poster presentation) Hepatology. 2008;48:4(suppl.):744A (abstract 977)

[7] Baraclude. Summary of Product Characteristics Available at: http://emea.euopa.eu/humandocs/PDFs/EPAR/baraclude/H-623-Pl-en.pdf Last viewed 24/03/09

[8] Shepherd J. et al. Entecavir for the treatment of chronic hepatitis B. Evidence review group report commissioned by the NHS R&D HTA Programme on behalf of NICE. 2008.