13 November 2008

[redacted]

Dear [redacted]

**Single Technology Appraisal – Tenofovir for the treatment of chronic hepatitis B**

The evidence Review Group, (SHTAC) has now had an opportunity to take a first look at the industry submission document and economic model submitted by Gilead. There are a number of issues and queries on which we are seeking your feedback at this early stage.

The comments and queries included in this letter are divided into two sections:

**A) Clarifications on effectiveness data**
These points are very important to enable us to understand the presented results and their impact on the model.

**B) Economic analysis**
These points are very important to enable us to make appropriate and relevant interpretations from the model, and to discuss a fair and rational appraisal of the model.

Both the Evidence Review Group and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Committee Meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by 28 November 2008.

Yours sincerely

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## Section A: Clarifications of the effectiveness data

### A1 Literature searching

A1.1 Please provide a copy of the full search strategy. Currently there is no indication of whether free text and/or subject index headings (e.g. MeSH in Medline) terms were used. If possible please can the strategy as run be supplied (e.g. that shows the number of hits generated by each line of the strategy). This will enable us to check the results of the search.

A1.2 Please specify the host system used for the Medline search (e.g. Ovid)

A1.3 Please clarify exactly which years were searched?.

A1.4 Were Embase, the Cochrane Central Register of Controlled Trials and MEIP (Medline in Process) searched?

A1.5 Were any search filters used to retrieve RCTs or cost effectiveness studies?

A1.6 We note that the database searches are current to 31st August 2007. Was an identical update search run on all the databases?

A1.7 The 'NewDrugFile' database is mentioned. Please specify whether the version used is hosted by Promedis

A1.8 Were ongoing trial databases searched (i.e. UKCRN, clinical trials.gov, controlled clinical trials.com in addition to NewDrugFile?)

### A2 Systematic review of clinical effectiveness

A2.1 In Figure 1 (Section 6.1, page 23) it reports that of 170 publications that met the criteria for the systematic review, there were 122 papers describing non-randomised studies, of which 46 non-randomised trials met the inclusion criteria for the systematic review. Does this mean that 76/122 studies were excluded, despite them meeting the criteria for the systematic review? Were the 46 non-randomised trials reported in a total of 122 papers?

A2.2 Please can you supply full bibliographical details of the 46 non-randomised trials included in the systematic review.

A2.3 Please specify whether any of the 170 publications meeting the inclusion criteria were duplicates.

A2.4 In Figure 1 (page 23) an asterisk appears in four of the boxes in the lower left hand corner. To what is this asterisk referring?

A2.5 On page 23 (section 6.1) it is mentioned that there are 7 RCTs of tenofovir, but in table 6.2.1 there are 8 listed. Was this a typographical error? In which case should there be 53 RCTs in total?

A2.6 Of the 52 RCTs that met the inclusion criteria for the wider systematic review, 23 met the criteria for the MTC. Please can you supply full bibliographical details and reasons for excluding the 29 that did not meet the criteria for the MTC.

A2.7 Page 81 (6.10.1.4): please clarify why the section of resistance surveillance in weeks 0-48 of studies 01202 and 0103 is marked as CIC, when the information has been or is due to be presented at EASL conference(s)?

**A3 Mixed Treatment Comparison (MTC)**

A3.1 On page 60 (Section 6.6.2) it is reported that 13 trials met the inclusion criteria for the MTC. This contradicts the figure of 23 given in Figure 1 (Section 6.1, page 23) and also given in Appendix 4. We presume this is a typographical error?

A3.2 Was there any critical appraisal of the studies included in the mixed treatment comparison? If so please can you supply details.

A3.3 The description of the inclusion criteria for the MTC is inconsistent between the main submission and Appendix 4. In particular on page 31 of Appendix 4 it says that 'HBeAg-positive, lamivudine-resistant/refractory with/without HIV co-infection' were eligible. This isn't mentioned in the main submission document. Please can you clarify what you mean by 'with/without', and why this only applied to this one subgroup? We presume that it was for sensitivity analysis purposes, but would like clarification.

A3.4 In Appendix 4 we presume that no table of the baseline characteristics / table of results for the lamivudine-refractory patients (similar to the tables for nucleoside naïve patients – Tables 5 and 6) was not supplied because there were no RCTs of tenofovir in this patient group and therefore full results of this analysis are not reported. We assume the same for HBeAg negative patients in nucleoside/nucleotide naïve patients as an MTC was not possible. Please can you confirm that this is the case.

## Section B: Economic Analysis

B1. In Section 7.1.1 it is stated that two cost-effectiveness evaluations were included in the review of cost-effectiveness, out of a total of 170 included publications. As the searching for clinical and cost-effectiveness studies appears to be combined please can clarification be given as to where these two studies fit in to Figure 1 in section 6.1. In Figure 1 the 170 publications are described as either being RCTs or non-randomised

studies, but no mention is made of cost-effectiveness studies (unless these are counted as being non-randomised studies?)

B2. In the model, the same mean age at start of treatment is assumed for HBeAg positive and HBeAg negative patients. However, Appendix 7 of the MS quotes figures for the "global population with CHB", drawn from a review on the natural history of CHB by Fattovich, giving a median age of 31 for HBeAg positive patients and of 40 for HBeAg negative patients. The Fattovich review also suggests that a larger proportion of HBeAg negative patients will have compensated cirrhosis (compared with HBeAg positive patients).

a) Please provide a rationale for assuming the same starting age (or alternatively the same time horizon) for both groups of patients?

b) Were there additional data from audit of patients attending the [redacted] hepatology clinic that would support this assumption?

c) Did the clinicians providing expert advice support the assumption, included in a footnote to Table 30 in the MS, that 50% of all patients with compensated cirrhosis were HBeAg negative?

B3. Please provide a rationale for using constant values for all-cause mortality, rather than age-specific values?

B4. Please explain how you derived the figure of 1.07% annual mortality for males and 1.09% annual mortality for women? These do not seem to correspond to the quoted life expectancies at age 38, from Scottish life tables, of 38.5 years (male) and 42.6 years (female). The ERG estimated annual mortality rates from these life expectancies (using the DEALE method) would be 2.60% (risk = 2.56%) for men and 2.35% (risk = 2.32%) for women.

B5. Please clarify whether there are any assumptions (implicit or explicit) in the model, regarding regression from compensated cirrhosis to CHB/ viral suppression?

a) Page 116 of the MS states that patients could not revert from compensated cirrhosis to active CHB or viral suppression, regardless of viral load or treatment. However the arrows between active CHB/ VS and CC/ CC with undetectable HBV DNA are two headed (suggesting movements in both directions and contradicting the statement on Page 116) – see Figure 1 below. Please clarify which approach was used in the model?

**Figure 1 – Transitions between compensated cirrhosis (compensated cirrhosis with detectable HBV DNA or compensated cirrhosis with less than 300 copies per millilitre HBV DNA) and active CHB/ Viral Suppression health states (as shown in the state transition diagram in the MS).**

**Figure 1a – extract for HBeAg positive patients**

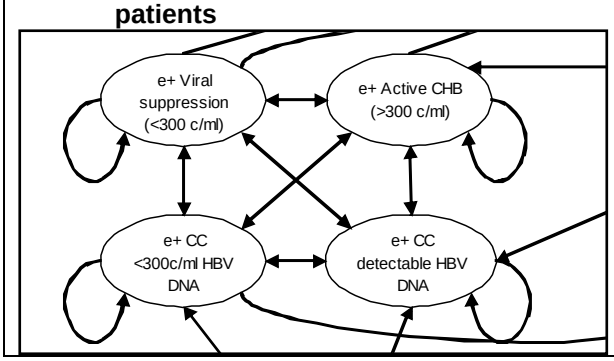
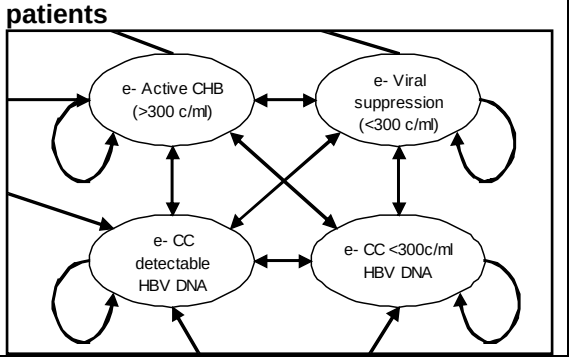



**Figure 1b – extract for HBeAg negative patients**




b) Please could you state whether patients who achieve HBeAg seroconversion from a compensated cirrhosis state (either compensated cirrhosis with detectable HBV DNA or compensated cirrhosis with less than 300 copies per millilitre HBV DNA) move to a compensated cirrhosis state or to active CHB when reactivating disease – i.e. does the model implicitly assume that HBeAg seroconversion is associated with regression of cirrhosis (by allowing previously cirrhotic patients to enter the CHB state) or does the model contain memory of seroconverted patients previous health state(s)?

c) If the model allows previously cirrhotic patients (who have seroconverted) to enter the CHB state on reactivation of disease, was this assumption based on observed data and/ or was this assumption clinically validated?

B6. Please can you provide a rationale for using data on the development of resistance to combination treatment from an abstract (Sung et al. J Hepatol. 2003;38(Suppl 2):25-6) given that the trial has now been reported in a full journal publication (Sung JJY, Lai JY, Zeuzem S, Chow WC, Heathcote EJ, Perrillo RP, et al. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. J Hepatol 2008;48:728–735), including up to two years of data? The full journal publication reports resistance at 1 year (on the combination of lamivudine and adefovi) as 9% (5/58), rather than 2% (1/49) as reported in the abstract. While the denominator for single agent (lamivudine) changes slightly in the full publication (from 49 to 51) the estimated proportion of patients developing resistance at 1 year was almost unchanged at 20% (10/51). The estimated relative risk of developing resistance at 1 year (combination versus single agent) of 0.1, based on the abstract data and as reported in the MS, increases to 0.44 based on the data reported in the full publication. At two years the proportion of patients with resistance were 43% (15/35) for single agent and 15% (6/41) for the combination.

B7. The section on utilities (7.2.8.3) refers to a poster by Ossa and colleagues and to a published paper by Levy and colleagues. Values used in model are taken from Ossa and colleagues rather than from the fully published study, but there is no discussion of the reason for this choice or any effect this may have on the model results. Could you supply the rationale for adopting the health state valuations from Ossa and colleagues, rather than the UK-specific values presented by Levy and colleagues?

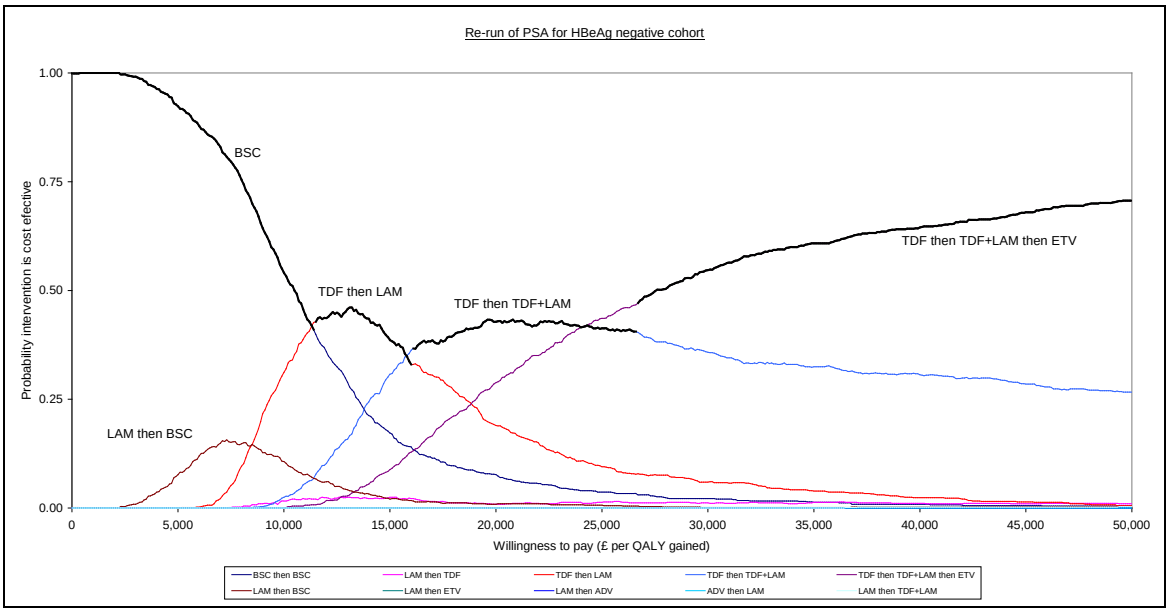
B8. There appear to be inconsistencies between Table 37 and Table 38 in the submission (and between Table 37 and the submitted electronic model). The inconsistencies are as follows:

- The row labels in Table 37 are consistent with Table 38. However many of the total cost and total QALY values are not consistent between the two tables.
- The row labels and content of Table 38 are consistent with the submitted electronic model.

It appears that there has been an error populating Table 37 – can you confirm that this is the case and that Table 38, and the submitted electronic model, contain the correct values?

B9. The cost effectiveness acceptability curves presented in Figure 15 of the MS, for the HBeAg negative population, do not appear to be correct (or consistent with data for the deterministic base case presented in Table 38). The ERG have re-run this analysis using the submitted electronic model, deriving CEACs and a cost effectiveness acceptability frontier as shown in Figure 2 below (the cost effectiveness acceptability frontier is shown by the heavy black curves, with associated labels indicating the treatment strategy yielding the maximum average net benefit at each willingness to pay threshold).

**Figure 2 – CEACs for HBeAg negative cohort, re-run PSA from the manufacturer's model**



a) Please can you confirm whether the CEACs and cost effectiveness acceptability frontier derived from the PSA conducted for the submission are correctly presented in Figure 15 of the MS or whether they are similar to those presented in Figure 2 above?

b) If the analysis presented in Figure 15 of the MS is correct, can you provide a rationale for why the ERG replication of this analysis using the submitted model (presented in Figure 2 above) is so different?

B10. There appear to be errors in the calculation of the mean ICERs for "TDF then LAM" relative to other treatment strategies in Table 43 of the MS. Examination of the electronic model suggests that calculations to derive mean ICERs (in cells DY4 to ER4 on the "Simulations" sheet) are based on maximum values (derived in cells H4 to DW4 the "Simulations" sheet) rather than averages.

**Table 1 - Mean ICERs for "TDF then LAM" relative to other treatment strategies as reported in MS and as re-calculated by ERG**

| Treatment strategy | ICER TDF then LAM vs other strategies as reported in MS | ICER TDF then LAM vs other strategies as calculated by ERG |
|---|---|---|
| BSC then BSC | £21,789 | £9,745 |
| LAM then TDF | £6,211 | £7,885 |
| TDF then LAM | - | |
| TDF then TDF+LAM | Dominant | £26,139 |
| TDF then TDF+LAM then ETV | Dominant | £26,226 |
| LAM then BSC | £17,726 | £10,557 |
| LAM then ETV | £5,912 | £3,056 |
| LAM then ADV | £5,961 | £3,491 |
| ADV then LAM | Dominant | Dominant |
| LAM then TDF+LAM | Dominant | £1,281 |
| TDF then BSC | £19,075 | £4,206 |
| TDF then ETV | Dominant | Dominant |
| LAM then ADV+LAM | Dominant | Dominant |
| ADV then TDF | Dominant | Dominant |
| ADV then TDF+LAM | Dominant | Dominant |
| ADV then ADV+LAM | Dominant | Dominant |
| ETV then LAM | Dominant | Dominant |
| ETV then TDF | Dominant | Dominant |
| ADV+LAM then TDF+LAM | Dominant | Dominant |
| ETV+ADV then LAM | Dominant | Dominant |

a) Please can you confirm that the calculation of mean ICERs presented in the MS is incorrect and that the calculations conducted by the ERG are correct?

b) The ERG have not been able to check the calculations for the HBeAg positive cohort as no spreadsheet containing the results for this cohort has been submitted and the submitted electronic model is setup to run probabilistic analysis only for HBeAg negative cohort. However, it is likely that these calculation errors also apply to the mean ICERs in Table 42 of the MS (please can you confirm)?

B11. When running the PSA for the submitted electronic model (which allows analysis of ten treatment strategies (BSC then BSC, LAM then TDF, TDF then LAM, TDF then TDF+LAM, TDF then TDF+LAM then ETV, LAM then BSC, LAM then ETV, LAM then ADV, ADV then LAM, LAM then TDF+LAM)) there appear to be errors in approximately 4% of simulations for some of the included treatment strategies (LAM then TDF, TDF then LAM, TDF then TDF+LAM, TDF then TDF+LAM then ETV, LAM then ADV, ADV then LAM, LAM then TDF+LAM). The ERG cannot investigate the cause of these errors as access to the visual basic code in the model has been password protected. All we can report is that around 4% of simulations for the above strategies have invalid values (reported as #NUM! in cells in the output area of the "Simulations" worksheet).

a) Please can you confirm whether or not you observed such errors in the output from the PSA conducted for the MS?

b) Please can you identify the cause of these errors in the electronic model submitted to NICE?

B12. Please provide instructions for running the model / PSA and a description of what is shown on each of the Excel worksheets.

a) Is it possible to run the model for a smaller number of scenarios, for example only scenarios 1-20, without access to the visual basic code?

b) Is it possible to run any of the scenarios on its own deterministically and if so where are the results shown?