NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Telbivudine for the treatment of chronic hepatitis B

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide additional information and clarification relating to systematic reviews carried out, clinical effectiveness and cost effectiveness data presented, clinical and cost parameters used in the economic model and methodology used to assess uncertainty in the economic results.

Licensed indication

Telbivudine (Sebivo, Novartis) is indicated for the treatment of chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

1 Key issues for consideration

Clinical effectiveness

- Which of the various surrogate markers of response to treatment best reflects long-term outcomes in CHB?
- What is the most appropriate place for telbivudine in the pathway of care?
- How will be telbivudine be used in clinical practice: as monotherapy or in combination with other agents?

- Are the statistically significant differences in clinical effectiveness outcomes between telbivudine and lamivudine clinically meaningful?
- How useful is the indirect comparison of telbivudine with entecavir via the common comparator of lamivudine in the assessment of clinical effectiveness?
- What is the Committee's view about the exclusion of interferon/pegylated interferon and adefovir dipivoxil from the assessment of clinical effectiveness?
- What is the Committee's view about the potential development of treatment resistance?
- What is the Committee's view on the relevance of the ethnic mix of the trial population compared with the UK CHB population?

Cost effectiveness

- What is the Committee's view on which model (viral load or seroconversion) used in the economic analyses is most appropriate?
- Is the exclusion of entecavir from the economic analyses based on the manufacturer's submission interpretation of the indirect comparison appropriate?
- What is the Committee's view of the concerns expressed by the ERG about the completeness and reliability of the data used to populate the economic models?
- Are the details provided about subgroups sufficiently robust to be used in the economic models (for example ALT levels greater than or equal to twice the upper limit of normal)?
- Does the Committee consider that the method used to deal with sparse data in the model is appropriate (that is, the selection and impact of the 'non-informative priors')?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with compensated liver disease and active CHB (that is, evidence of viral replication and active liver inflammation)
Intervention	Telbivudine monotherapy
Comparators	Lamivudine (as first-line oral antiviral treatment)
Outcomes	HBeAg/HBsAg seroconversion rate Virological response (HBV DNA levels) Histological improvement (in inflammation and fibrosis) Biochemical responses (for example, serum ALT levels) Development of viral resistance Time to treatment failure Survival Health-related quality of life Adverse effects of treatment
Economic evaluation	Two transition-state models presented: a seroconversion model (applicable to only HBeAg-positive patients) and a viral load model (applicable to both HBeAg-positive and -negative patients).
ALT: alanine aminotransferase, CHB; chronic hepatitis B, HBeAg: hepatitis B e antigen, HBsAg: Hepatitis B surface antigen, HBV: hepatitis.	

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered that the population described in the manufacturer's submission reflected UK clinical practice for the treatment of CHB, and appeared to be appropriate for the NHS. The majority of participants in the trial were Asian, with approximately 50% being Chinese Asian, but the ERG concluded that this did not impact on the generalisability of the evidence to the UK CHB population, because majority of new cases in the UK are immigrants from Eastern Europe and the Far East.

1.2.2 Intervention

The intervention in the manufacturer's submission is telbivudine monotherapy for CHB. This is within the UK marketing authorisation for telbivudine and is appropriate for use in the NHS.

1.2.3 Comparators

The manufacturer's submission contained evidence from randomised controlled trials (RCTs) directly comparing telbivudine with lamivudine and indirectly comparing telbivudine with entecavir (via lamivudine). Other comparators identified in the original scope – namely interferon alfa/peginterferon alfa-2a and adefovir dipivoxil – were not included in the manufacturer's submission because of the intended place of telbivudine in the treatment pathway; that is, as a first-line oral therapy. The ERG considered this deviation from the scope as a weakness of the manufacturer's submission.

1.2.4 Outcomes

All of the outcomes identified in the scope were assessed in the manufacturer's submission, except for time to treatment failure, health-related quality of life (HRQoL) and survival. The outcomes that were included in the manufacturer's submission were considered appropriate and clinically meaningful by the ERG.

1.2.5 Economic evaluation

The manufacturer's submission provided two economic models: a viral load model (the manufacturer's preferred approach) and a seroconversion model. Both were state-transition models.

The ERG noted that the structure of the models and the methodology employed were consistent with previous economic evaluations of antiviral treatment of CHB and were appropriate. No deterministic results were reported by the manufacturers.

1.3 Statements from professional/patient groups and nominated experts

The desired treatment outcome for CHB is rapid control of hepatitis B virus (HBV) replication as indicated by HBV DNA being undetectable by a sensitive polymerase chain reaction (PCR) assay. However, treatment endpoints are generally not clearly defined, and differ between hepatitis B e antigen (HBeAg)-positive and HBeAg-negative disease. In HBeAg-positive disease, the aim of antiviral treatment is loss of HBeAg and durable seroconversion to anti-HBe, which may be considered as a treatment stopping rule. However, treatment with nucleoside analogues should continue for at least 6 months after loss of HBeAg and the majority of patients require long-term maintenance suppressive therapy. A reduction of HBV DNA concentrations to less than 10^4 or 10^5 copies per ml, or to levels undetectable by sensitive PCR assay (less than 200 copies per ml) may become the benchmark.

In HBeAg-negative disease (or 'precore mutant' HBV), treatment aims to reduce serum ALT and HBV DNA levels with accompanying histological improvement and maintenance of response (defined by low viral load during therapy without treatment resistance). Finite courses of treatment are less commonly used in HBeAg-negative disease because of higher rates of relapse. Disease progression may be halted if HBV DNA remains suppressed and resistance and/or relapse does not occur. Successful treatment with antiviral therapy is characterised by reduction of HBV DNA to less than 10^4 copies per ml, or to levels undetectable by sensitive PCR.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

A summary of the clinical results after 104 weeks of follow-up from the registration RCT, NV-02B-007 (GLOBE), is presented in table 1 (see pages

44–50 of the manufacturer's submission and pages 35–41 of the ERG report for full details).

Table 1. GLOBE randomised controlled trial – results at week 104

	HBeAg-positive disease		HBeAg-negative disease	
GLOBE RCT Outcome measure	**Telbivudine (600 mg) (n = 458)**	**Lamivudine (100 mg) (n = 463)**	**Telbivudine (600 mg) (n = 222)**	**Lamivudine (100 mg) (n = 224)**
% achieving therapeutic response	63.3	48.2	77.5	66.1
% absolute difference in response	15.1		11.4	
95% confidence intervals	8.6 to 21.6		2.9 to 19.9	
p value	< 0.0001		0.0069	
Mean HBV DNA (reduction from baseline): log_{10} copies/ml (± SEM)[1]	–5.74 (0.15)	–4.42 (0.15)	–5.00 (0.15)	–4.17 (0.16)
p value	< 0.0001		0.0002	
Proportion of patients with PCR non-detectable HBV DNA (%)	55.6	38.5	82.0	56.7
p value	< 0.0001		< 0.0001	
ALT normalisation (%)	69.5	61.7	77.8	70.1
p value	0.0135		0.0725	
HBeAg loss (%)[2]	35.2	29.2	N/A	N/A
p value	0.0556			
HBeAg seroconversion[3] (%)	29.6	24.7	N/A	N/A
p value	0.0947			

[1] SEM is standard error of mean
[2] HBeAg loss refers to loss of detectable HBeAg where HBeAg was detected at baseline
[3] HBeAg seroconversion refers to loss of detectable HBeAg (if present at baseline) together with gain or appearance of detectable antibodies to HBeAg (HBeAb)

	HBeAg-positive disease		HBeAg-negative disease	
GLOBE RCT **Outcome measure**	**Telbivudine (600 mg) (n = 458)**	**Lamivudine (100 mg) (n = 463)**	**Telbivudine (600 mg) (n = 222)**	**Lamivudine (100 mg) (n = 224)**
HBeAg seroconversion (%) as per guidelines[4]	36.2	27.9	N/A	N/A
p value	0.0268			
Virological breakthrough per protocol[5] (%)	23.3	37.1	8.4	19.7
p value	< 0.0001		0.0013	
HBV resistance per protocol (%)	21.7	34.1	8.4	20.2
p value	< 0.0001		0.0008	
Virological breakthrough > 1 log above nadir[6] (%)	28.6	45.5	12.2	30.4
p value	< 0.001		< 0.0001	
HBV resistance > 1 log above nadir (%)	25.1	39.5	10.8	25.9
p value	< 0.0001		< 0.0001	

[4] In patients with serum alanine aminotransferase levels ≥ 2 × upper limit of normal

[5] Virological breakthrough per protocol is defined as an increase in HBV DNA to ≥ 5 $\log^{10}$ copies/ml on two consecutive occasions in patients who had previously achieved post-baseline virological response

[6] '1 log above nadir' virological breakthrough is defined as confirmed HBV DNA increase of ≥ 1 $\log_{10}$ copies/ml above nadir HBV DNA (the lowest post-baseline HBV DNA level achieved) in those patients with a confirmed treatment response (that is, ≥ 1 log reduction in HBV DNA)

2.2 Evidence Review Group comments

The ERG considered that the manufacturer presented an unbiased estimate of the anti-viral treatment efficacy of telbivudine compared with lamivudine, based on the results from one trial of reasonable methodological quality (the GLOBE trial). The ERG noted that some comparators and outcome measures defined in the original scope were not addressed by the manufacturer. Some other issues and areas of uncertainty were identified by the ERG. These are described in sections 2.2.1 and 2.2.2.

2.2.1 Direct comparison

- The ERG identified one potentially relevant study that was excluded from the manufacturer's systematic review. However, the ERG concluded that the results of this RCT would not have substantially affected the conclusions of the manufacturer's submission.
- Although statistically significant advantages were demonstrated for telbivudine compared with lamivudine for a number of outcomes, the ERG queried whether these differences are clinically meaningful.
- There was no discussion of the high viral resistance rate of telbivudine and the clinical impact of this on people with CHB. The ERG suggests that these resistance rates and subsequent viral breakthrough may be clinically unacceptable. It is acknowledged, however, that the viral resistance rates for telbivudine are numerically lower than those for lamivudine, a drug that is commonly used as the first-line oral therapy.

2.2.2 Indirect comparison

- The ERG felt that the manufacturers provided inadequate descriptions of the methodology used for the indirect comparison with entecavir. The evidence network was not fully informed and quality was not assessed using appropriate systematic review methods.
- There were differences between the trials that were used in the indirect comparison, such as: primary outcome of interest; racial composition of the

trial populations, HBV genotype; and previous IFN therapy. The ERG acknowledged that these differences could present difficulties for any comparisons between trials.

- The indirect comparison was mainly based on a visual 'naive' comparison of the key efficacy outcomes from the identified trials. The ERG felt that conclusions drawn from this comparison should be treated with caution.
- The manufacturer performed a statistical indirect comparison and presented it in an appendix to the main report. This comparison suggested there were no statistically significant differences in effectiveness between telbivudine and entecavir. The ERG felt that this comparison was invalid and stated that it should be viewed with caution.
- The viral resistance rates of entecavir and telbivudine were not considered in the indirect comparison. The ERG considered this omission a problem, given that the published resistance rates for entecavir are lower than those for telbivudine and the clinical relevance of differences in viral resistance rates.

2.3 Statements from professional/patient groups and nominated experts

The submissions from the clinical experts provided further testimony on the following:

- A phase II study in HBeAg-positive disease that compared two different doses of telbivudine (400 mg/day and 600 mg/day), lamivudine (100 mg/day) and combinations of lamivudine and telbivudine, noting that the combination treatment was not found to be superior to telbivudine monotherapy in terms of reduction in HBV DNA levels, levels of undetectable HBV DNA or HBeAg loss.
- The finding in the GLOBE trial that treatment resistance after 2 years was rare in HBeAg-positive patients who were HBV DNA negative at 24 weeks of therapy (4%), compared with patients who had detectable HBV DNA

levels at 24 weeks (25–30%). A similar trend was observed in HBeAg-negative patients.

- Differences between viral mutations associated with telbivudine and lamivudine resistance, because of differences in pathways for selection of tyrosine–methionine–aspartate-mediated HBV resistance.

The clinical experts stated that:

- Telbivudine has been proven to be a safe and potent oral nucleoside analogue and that several large RCTs have shown that it results in greater log suppression of HBV at 1 year of treatment than lamivudine and adefovir dipivoxil.
- Treatment resistance to telbivudine emerges at a slower rate than to lamivudine, but is significant in patients who fail to show early viral response.
- There will be an increasing need for diagnostic services for screening patients for suitability for treatment with nucleoside analogues and for monitoring the efficacy of these agents (by viral load measurements), as well as resistance testing services.
- Telbivudine cannot be used in lamivudine-resistant patients; the de novo combination is ineffective and telbivudine shows cross-resistance with lamivudine.
- Correlation has been shown between maximal early virological suppression and one-year outcomes and the likelihood of treatment resistance, which calls into question the scope and potential shortcomings of the use of nucleoside analogue monotherapy in patients with high levels of HBV replication whose viral loads do not decline rapidly.
- In patients with high viral loads and in those with decompensated cirrhosis, rapid suppression of HBV DNA replication will be beneficial and thus suitably evaluated combination treatments or monotherapy agents with low rates of resistance would confer a low risk of primary treatment failure or resistance.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

Base-case incremental cost-effectiveness ratios (ICERs) from the manufacturer's state-transition economic model, based on viral load, are shown in tables 2 to 5. These results refer to an amended base-case analysis following a request for clarification from the ERG regarding errors identified in the viral load models. In response the manufacturer submitted a revised set of results and updated versions of the electronic models. The ICERs reported are for telbivudine followed by best supportive care (BSC) if appropriate compared with lamivudine followed by BSC if appropriate, and are derived from a deterministic analysis, using a lifetime horizon.

Due to the sparse nature of the data, a large number of raw transition probabilities were zero. To explore the effects of this, 'non-informative priors' of 0.0 or 0.5 were added to all states where there was one or more possible transitions with zero observations (see page 98–100 of the manufacturer's submission and pages 111–114 of the ERG report for further details).

Table 2. HBeAg-positive patients (with 'non-informative prior' = 0.0)

	Lifetime costs (£)	Lifetime QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Telbivudine	56,669	16.43	22,456	1.83	12,278
Lamivudine	34,214	14.60			
ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.					

Table 3. HBeAg-positive patients (with 'non-informative prior' = 0.5)

	Lifetime costs (£)	Lifetime QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Telbivudine	32,333	20.01	11,961	1.38	8,669
Lamivudine	20,372	18.63			
ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.					

Table 4. HBeAg-negative patients (with 'non-informative prior' = 0.0)

	Lifetime costs (£)	Lifetime QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Telbivudine	77,429	15.06	41,012	2.01	20,383
Lamivudine	36,417	13.05			

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.

Table 5. HBeAg-negative patients (with 'non-informative prior' = 0.5)

	Lifetime costs (£)	Lifetime QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Telbivudine	43,823	18.82	26,683	0.46	57,419
Lamivudine	17,141	18.35			

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year.

Probabilistic base-case ICERs from the manufacturer's economic model based on viral load are shown in tables 6 and 7. These results refer to the amended base-case analysis and are derived from a probabilistic sensitivity analysis (PSA). The ICERs reported are for telbivudine followed by BSC if appropriate compared with lamivudine followed by BSC if appropriate. See page 98–100 of the manufacturer's submission and pages 111–114 of the ERG report for further details.

Table 6. Viral load based on PSA (with 'non-informative prior' = 0.0)

	Mean incremental costs from PSA analyses	Mean incremental QALYs from PSA analyses	Mean ICER (95% CI)
HBeAg-positive disease	£23,983	1.56	£15,377 (£6,643 – £432,748)
HBeAg-negative disease	£41,910	2.07	£20,256 (£15,237 – £66,459)

CI: confidence interval, ICER: incremental cost-effectiveness ratio, PSA: probabilistic sensitivity analysis, QALY: quality-adjusted life year.

Table 7. Viral load based on PSA (with non-informative prior = 0.5)

	Mean incremental costs from PSA analyses	Mean incremental QALYs from PSA analyses	Mean ICER (95% CI)
HBeAg-positive disease	£12,479	1.46	£8,542 (£291 – dominated)
HBeAg-negative disease	£26,883	0.97	£27,801 (£2,000 – dominated)

CI: confidence interval, ICER: incremental cost-effectiveness ratio, PSA: probabilistic sensitivity analysis, QALY: quality-adjusted life year.

Base-case ICERs from the manufacturer's economic model based on HBeAg seroconversion are shown in tables 8 and 9. The analyses are only applicable to HBeAg-positive disease and are derived from PSA analyses, using a lifetime horizon. The analyses are based on a number of treatment algorithms. See page 98–100 of the manufacturer's submission and pages 111–114 of the ERG report for further details.

Table 8. Key to treatment algorithms used in the seroconversion model

Treatment algorithm	First-line treatment	Second-line treatment	Third-line treatment
0	BSC	BSC	BSC
1	Lamivudine	BSC	BSC
2	Telbivudine	BSC	BSC
3	Adefovir dipivoxil	BSC	BSC
4	Lamivudine	Adefovir dipivoxil	BSC
5	Telbivudine	Adefovir dipivoxil	BSC
6	Adefovir dipivoxil	Lamivudine	BSC
7	Adefovir dipivoxil	Telbivudine	BSC

BSC: best supportive care.

Table 9. Seroconversion model based on PSA

Treatment algorithm vs algorithm 0	Mean incremental costs	Mean incremental QALYs	Mean ICER (95% CI)
1	£503,059	63.78	£7,887 (£3,942 – £16,717)
2	£1,529,867	115.96	£13,193 (£7,788 – £25,194)
3	£2,136,201	117.63	£18,160 (£11,490 – £30,160)
4	£1,667,090	113.75	£14,655 (£8,599 – £25,242)
5	£2,345,968	149.58	£15,684 (£9,491 – £28,151)
6	£2,247,279	129.17	£17,398 (£11,063 – £28,322)
7	£2,512,060	136.61	£18,388 (£11,707 – £30,357)

CI: confidence interval, ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

3.2 Evidence Review Group comments

Overall, the ERG considered that the approach taken by the manufacturer to assess the cost effectiveness in this patient group was reasonable and is consistent with the methods adopted in previous economic evaluations of antiviral treatment for CHB. However, a number of issues and areas of uncertainty were identified by the ERG:

- Entecavir was not included in the economic models, based on the assumed equivalence of entecavir and telbivudine, derived from the 'naive' indirect comparison. The ERG did not consider this exclusion to be justified because of methodological concerns about the indirect comparison, and because of the possible better resistance profile of entecavir relative to telbivudine. Lack of statistically significant differences are not considered by the ERG to be a valid reason for exclusion of a comparator.

- Evidence on the comparative clinical and cost effectiveness of adefovir dipivoxil was not adequately identified; no searches for indirect evidence were undertaken and there was no critical assessment of the data taken from 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B' (NICE technology appraisal guidance 96). The manufacturer made no attempts to justify or investigate its assumptions about the clinical or cost effectiveness of adefovir dipivoxil.

- The ERG believed that there was insufficient discussion about the method for dealing with sparse data and the impact of the values adopted for the 'non-informative priors' in the viral load model. The ERG concluded that this made critical appraisal of the use of the two priors very difficult, but notes that the impact of the priors indicates that the sparse nature of the data may be a problem. The ERG noted that investigation into statistical modelling alternatives may have been appropriate to reduce the impact of the sparseness of the data for some transitions included in the model.

- The economic models use data from a subgroup of the participants in the GLOBE trial, with ALT levels at two or more times the upper limit of normal, to estimate the clinical effectiveness of telbivudine and lamivudine. However, this subgroup was not presented in detail in the discussion of clinical effectiveness including no specific baseline trial information or critical appraisal of treatment efficacy in this subgroup. Therefore, the key clinical-effectiveness data in this economic model could not be critically appraised by the ERG.

- The ERG found discrepancies between the input values for the viral load model and the values used in the submitted electronic models (this was in addition to the errors that were corrected after clarification). Replacing values in the models with those from the appendices led to a lower QALY gain for telbivudine compared with lamivudine and a less favourable ICER for telbivudine compared with lamivudine. The ERG note that the submitted economic models, particularly the viral load model, were complex and lacked transparency, and that limited discussion of the data validity was provided in the manufacturer's submission. This means that the ERG cannot be certain if some differences are due to missing or incorrect data or real differences in efficacy.

- The ERG commented that the manufacturer's submission contained insufficient discussion of uncertainty: no deterministic models were presented, and the details of the PSA were presented inadequately in the main body of the submission. The ERG feels that this results in difficulty in identifying the key drivers in the economic models. The ERG also noted that the manufacturer's submission did not report any one-way sensitivity analyses, which they viewed as a weakness of the submission; however, the ERG was able to produce one-way sensitivity analyses (see pages 69–73 of the ERG report for full details).

- There is insufficient discussion of the risk equations used to model progression to advanced liver disease in the viral load model, and there is a

lack of information presented on total costs for telbivudine and lamivudine. The ERG feels that this is a weakness of the manufacturer's submission.

3.3 Further considerations following premeeting briefing teleconference

NICE published guidance on the use of peginterferon alfa and adefovir dipivoxil in 2006 (NICE technology appraisal guidance 96). This makes the following recommendations:

1.1 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg positive or HBeAg negative), within its licensed indications.

1.2 Adefovir dipivoxil is recommended as an option for the treatment of adults with chronic hepatitis B (HBeAg positive or HBeAg negative) within its licensed indications if:

- treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
- a relapse occurs after successful initial treatment, or
- treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.

1.3 Adefovir dipivoxil should not normally be given before treatment with lamivudine. It may be used either alone or in combination with lamivudine when:

- treatment with lamivudine has resulted in viral resistance, or
- lamivudine resistance is likely to occur rapidly (for example, in the presence of highly replicative hepatitis B disease), and development of lamivudine resistance is likely to have an adverse outcome (for example, if a flare of the infection is likely to precipitate decompensated liver disease).

1.4 Drug treatment with peginterferon alfa-2a or adefovir dipivoxil should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a general practitioner is appropriate.

At the premeeting briefing teleconference the following additional issues were considered:

- How do the comparators considered in this appraisal relate to published NICE guidance and what is the likely place of telbivudine in the treatment pathway?
- What are the long-term concerns about the emergence of resistance?
- What is the best surrogate marker for the purposes of modelling long-term outcomes?

4 Authors

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2 Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The ERG report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Hartwell D, Jones J, Harris P, et al. Telbivudine as treatment for chronic hepatitis B, February 2008.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor:

- Novartis Pharmaceuticals

II Professional/specialist, patient/carer and other groups

- Association of Clinical Microbiologists
- British Society for Gastroenterology
- Queen Mary's School of Medicine, Barts and The London
- Royal College of Pathologists
- Royal College of Physicians
- Royal Free and University College School of Medicine

C Additional references used:

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006).