NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Entecavir 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 the following information:

Further details of the literature search methodology for the mixed treatment comparison; clarification of the comparators used; number of trials included and whether testing for heterogeneity was undertaken; and clarification of the information sources used to estimate some of the health effects.

Licensed indication

Entecavir (Baraclude, Bristol-Myers Squibb) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This indication is based on clinical trial data in patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative HBV infection, nucleoside-naive patients and patients with lamivudine-refractory hepatitis B.

Key issues for consideration

Clinical effectiveness

- Which of the various surrogate markers of response to treatment best reflect long-term outcomes in chronic hepatitis (CHB)?
- What is the most appropriate place for entecavir in the pathway of care?
- How will be entecavir be used in clinical practice: as monotherapy or in combination with other agents?
- What is the Committee's view of the potential for viral resistance with entecavir in the treatment of CHB?
- How useful are the findings of the network meta-analysis in drawing comparisons between treatments?
- What is the Committee's view on the lack of comparison with the currently recommended agents, adefovir dipivoxil and peginterferon alfa-2a (NICE technology appraisal 96)?

Cost effectiveness

- What is the optimum treatment duration for HBeAg-positive disease? Is the assumption in the model of a 2-year period of antiviral treatment valid?
- What is the optimum treatment duration for HBeAg-negative disease? Is the assumption in the model of a 5-year period of antiviral treatment valid?
- What is the Committee's view of the assumption in the model that no patients eligible for treatment would present with compensated cirrhosis? Is this an accurate reflection of clinical practice?
- What is the Committee's view of the assumption in the model that patients who progress to active cirrhosis stop receiving treatment for CHB? Is this an accurate reflection of clinical practice?
- Considering the ERG univariate sensitivity and scenario analyses, what is the Committee's view on the transition probabilities used in the model?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adult patients with compensated liver disease and active CHB (that is, evidence of viral replication and active liver inflammation)
Intervention	Entecavir alone
Comparators	Interferon alfa-2a and -2b, peginterferon alfa-2a (PegINF), lamivudine, adefovir dipivoxil, telbivudine
Outcomes	HBeAg/hepatitis B surface antigen (HBsAg) seroconversion rate Virological response (hepatitis B virus [HBV] DNA) Histological improvement (inflammation and fibrosis) Biochemical response (for example, ALT levels) Development of viral resistance Time to treatment failure Survival Health-related quality of life (HRQoL) Adverse effects of treatment
Economic evaluation	The cost effectiveness of treatment with entecavir will be expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. The time horizon for the economic evaluation will reflect the chronic nature of hepatitis B; analyses will be presented for a lifetime horizon. The analyses will be conducted in accordance with the NICE reference case for economic evaluation. Costs will be considered from an NHS and personal social services (PSS) perspective.

1.2 Evidence Review Group comments

1.2.1 Population

The Evidence Review Group (ERG) was satisfied that the population specified matches the one in the appraisal scope and the licensed indication, and is appropriate for the NHS. The manufacturer's submission also distinguishes

between treatment-naive patients who have either HBeAg-positive or HBeAg-negative disease and patients with disease resistant to nucleoside analogue treatment, in accordance with the scope.

1.2.2 Intervention

The intervention described in the decision problem is entecavir monotherapy, which, the ERG agree, reflects the marketing authorisation and is appropriate for the NHS. However, the ERG notes that, according to the scope for this appraisal, the intervention could also be entecavir in combination with other therapies. It is not clear whether the absence of mention of combination therapy in the marketing authorisation prohibits such use, and none of the randomised controlled trials (RCTs) of entecavir identified in the submission evaluated its use in combination with other drugs. According to expert clinical opinion sought by the ERG, entecavir is currently used in some parts of England and Wales, although generally not as a first-line treatment. Clinical opinion also suggests that for patients whose disease has failed to respond, or whose disease has relapsed after treatment with interferon or peginterferon alfa-2a (PegINF), it would be advantageous to proceed directly to a combination of entecavir and another nucleoside or nucleotide analogue drug.

1.2.3 Comparators

The comparators listed in the decision problem reflect those in the scope of the appraisal and are all appropriate to the NHS.

1.2.4 Outcomes

The outcomes listed in the decision problem reflect those in the scope of the appraisal. All meaningful clinical outcomes have been included. The ERG accepted the manufacturer's justification that the outcome 'viral suppression' is more appropriate for patients in whom HBeAg seroconversion is unlikely to occur (for example, where HBeAg-positive disease exists in patients who have not seroconverted or who have relapsed following earlier treatment) or for whom it is not applicable (HBeAg-negative disease).

1.2.5 Economic evaluation

The ERG said that the manufacturer's approach to economic modelling was generally reasonable, but that some unjustified assumptions in the model had resulted in an overestimate of the cost effectiveness.

1.3 Statements from professional/patient groups and nominated experts

The statements note that interferons and/or anti-viral drugs are currently used as first-line treatment for CHB, but optimal management strategies are unclear. The clinical experts said that the most common standard practice is initially to prescribe peginterferon alfa-2a for HBeAg-positive and HBeAg-negative cases for up to 12 months, which is in accordance with current NICE technology appraisal guidance (TA96). In cases where adequate and/or sustained virological response was not achieved (that is, HBV DNA ≥ 10^7copies/ml), it was stated that anti-viral agents would be prescribed either alone or as combined therapy. Standard practice is to prescribe entecavir as monotherapy and lamivudine/adefovir dipivoxil in combination. One clinical expert pointed out that despite NICE guidance, some physicians will not prescribe interferons and prefer to go directly to the use of anti-viral agents.

The clinical experts did not specify any disadvantages in prescribing entecavir compared with any of the other available therapies.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer identified 12 RCTs comparing entecavir with lamivudine, five of which met the criteria for inclusion in the review. All these five studies were double-blind RCTs, which were published in peer-reviewed journals. Four of the studies were carried out in the UK and one in China.

Table 1 gives details of the main results of the five individual RCTs. Entecavir was found to have superior efficacy to lamivudine in both HBeAg-positive and HBeAg-negative disease in both nucleoside-analogue-naive and lamivudine-refractory populations.

There were no statistically significant differences between entecavir and lamivudine in the number of patients achieving seroconversion at 48 weeks.

The manufacturer explained that resistance data from RCTs were not available. Data from descriptive studies presented in the MS showed that entecavir had a lower rate of genotype resistance than lamivudine, telbivudine and adefovir dipivoxil at 2, 3 and 4 years, and only a very slightly higher rate than adefovir dipivoxil at 1 year (adefovir dipivoxil 0%, entecavir 0.2%). For further details, see the MS, page 86.

None of the RCTs included in the MS reported health-related quality of life (HRQoL).

The manufacturer pointed out that, although there were no trials that included all treatment options in any of the patient populations, a series of network meta-analyses was conducted for nucleoside-naive patients (see pages 82–85 of the MS for a description of methodologies used, and pages 43–46 of the ERG report for critiques of this analysis). The results of the network meta-analysis showed that for HBeAg positive patients, entecavir had a significantly higher predicted probability of HBV-DNA response than all comparators and an equivalent predicted probability of serocoversion to all comparators at 1- and 2- years. Entecavir also had a significantly higher predicted probability of ALT normalisation than lamivudine (at both years) and peginterferon alfa-2a (year one), and was reported to be 'equivalent' to telbivudine (at both years). Entecavir had a significantly higher predicted probability of histological improvement compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. peginterferon alfa-2a was omitted from this analysis).

For HBeAg negative disease, entecavir had a significantly higher predicted probability of HBV DNA response at years one and two compared with lamivudine and peginterferon alfa-2a, and was reported to be equivalent to telbivudine at both years. Entecavir had a significantly higher predicted probability of ALT normalisation than all comparators at year one, but appeared similar to comparators at year two. Entecavir had a significantly higher predicted probability of histological improvement compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. peginterferon alfa-2a was omitted from this analysis).

The manufacturer pointed out that the available RCTs for HBeAg-positive, lamivudine-resistant disease tended to be smaller so the likelihood of no events occurring in one of the arms was much higher. As a result, while there were some possible evidence networks, these would not produce meaningful results. The manufacturer therefore carried out a 'simple' indirect comparison (see page 86 of the MS for a description of methodologies, and page 46 of the ERG report for critiques of this analysis). The results (table 5.1 of the MS) showed that entecavir treatment produced a higher rate of undetectable viral load, histological improvement and ALT normalisation than lamivudine, peginterferon alfa-2a and telbivudine.

Table 1 Results of the five included randomised controlled trials at 48 weeks – comparisons of entecavir (ENT) and lamivudine (LAM).

Study No.	Population	N	Virological response [1]		Histological response [2]		Biochemical response[3]	
			ENT v LAM % (p value)	Absolute difference (percentage points) ENT – LAM (95% CI)	ENT v LAM % (p value)	Absolute difference (percentage points) ENT – LAM (95% CI)	ENT v LAM % (p value)	Absolute difference (percentage points) ENT – LAM (95% CI)
023	Nucleoside-analogue-naive, HBeAg[4]-positive	446	74 v 38 (NR)	NR	NR	NR	89 v 78	NR
022	Nucleoside-analogue-naive, HBeAg-positive	709	67 v 36 (< 0.001)	30.3 (23.3 to 37.3)	72 v 62 (0.009)	9.9 (2.6 to 17.2)	68 v 60 (0.020)	8.4 (1.3 to 15.4)
023	Nucleoside-analogue-naive, HBeAg-negative	73	94 v 73 (NR)	NR	NR	NR	94 v 78	NR
027	Nucleoside-analogue-naive, HBeAg-negative	638	90 v 72 (< 0.001)	18.3 (12.3, 24.2)	NR	NR	78 v 71 (0.045)	6.9 (0.2 to 13.7)
026	Lamivudine-refractory, HBeAg-positive	286	19 v 1 (< 0.0001)	18.0 (11 to 24.5)	NR	NR	61 v 15 (< 0.0001)	51.7 (35.9 to 55.8)
014	Lamivudine-refractory, mixed HBeAg-positive and negative	286	HBV DNA < 400 copies/ml 26 v 4 (< 0.01)	NR	NR	NR	ALT < 1.25×ULN 68 v 6 (< 0.0001)	NR

[1]Hepatitis B virus (HBV) DNA < 300 copies/ml, [2] ≥ 2 point decrease in the Knodell necroinflammatory score with no worsening of fibrosis (≥ 1 point increase in Knodell fibrosis score), [3] alanine aminotransferase [ALT] ≤ 1.0×upper limit of normal [ULN]), NR =not reported [4]HBeAg; hepatitis B e antigen

2.2 Evidence Review Group comments

The ERG believed that the search process for clinical effectiveness studies reported by the manufacturer was generally comprehensive but noted that the search strategy was not fully reproducible because of limitations in reporting (see the ERG report, page 20, for further details).

The information presented in the manufacturer's systematic review was thought to be representative of the information in the published journal articles, and the trials included in the mixed treatment comparison appeared to be applicable to the decision problem.

The ERG also noted that there was no discussion regarding the similarity of the trials included in the mixed treatment comparison. Given the time period over which they were conducted, it would be reasonable to assume that there would be methodological differences as a consequence of technological innovations – for example, in HBV DNA assays. Furthermore, there was no assessment or discussion of heterogeneity (statistical or otherwise). The ERG asked the manufacturer to clarify whether heterogeneity had been assessed. The manufacturer clarified that there were insufficient data to allow a reliable estimate of a random effects variance to be obtained.

The ERG commented on the paucity of outcome data for year 2 treatment. The entecavir year 2 data presented was unpublished and has not been subject to external peer review.

The ERG considered that the results of the mixed treatment comparison were uncertain and should be interpreted with caution (see page 45 of the ERG report for a summary of their concerns).

2.3 Statements from professional/patient groups and nominated experts

There was consensus among the clinical experts and professional organisations that the RCTs showed that entecavir has greater efficacy and

lower resistance rates compared to the other available treatments. There was also consensus that entecavir would be tolerated by the majority of patients. The clinical experts also stated that viral resistance is a significant problem with current oral antiviral agents and that there are relatively few agents available for the management of chronic HBV. Some patients may develop multi-resistant viral strains that are, effectively, untreatable.

It was also pointed out that some patients with HBeAg-positive HBV may prefer an oral drug, such as entecavir, to an injectable drug such as peginterferon alfa-2a.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer submitted two Markov models (one for HBeAg-positive and one for HBeAg-negative disease). The HBeAg-positive disease model consisted of 14 health states that were defined as untreated CHB, spontaneous HBeAg seroconversion, HBsAg loss, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, post-liver transplantation, treated CHB, treatment-induced HBeAg seroconversion and death. The HBeAg-negative disease model also differentiates between response to initial treatment and response to salvage therapy, resulting in 15 health states. The models were designed to compare entecavir with lamivudine, peginterferon alfa-2a and telbivudine, and both had a lifetime horizon. For further details, see the MS, page 105.

The ERG said that the manufacturer's approach to modelling was generally reasonable and the models were internally and externally consistent, subject to some uncertainties (see the ERG's comments on the mixed treatment comparison in section 2.2 of this report).

The ERG said that the disease progression pathways assumed in the models were generally consistent with the natural history of CHB, although there were concerns about some of the structural assumptions (see the ERG's summary of the uncertainties in section 3.2 of this report) and the validity of the interpretation of the epidemiological evidence used (Fattovich et al 2002 MS pg 113) to derive probability values.

For further details, see pages 108–117 of the MS for a description of the model, and pages 9–13 of the ERG report for a summary and critique.

Table 2 Base-case results for the manufacturer's economic analysis; entecavir as first-line antiviral therapy in HBeAg-positive disease (2 yr treatment duration)

Comparison	Incremental QALY[1]	Incremental cost	ICER[2]
Entecavir v lamivudine	0.23	£3261	£14,329[3]
Entecavir v PegINF	0.20	£1649	£8403[3]
Entecavir v telbivudine	0.00	£187	telbivudine dominant

[1]QALY, quality-adjusted life year; [2]ICER, incremental cost-effectiveness ratio;
[3]The outcome of dividing incremental cost by incremental QALY will produce a result that is different from the reported ICERs due to the rounding effect

Table 3 Base-case results for the manufacturer's economic analysis; entecavir as first-line antiviral therapy in HBeAg-negative disease (5 yr treatment duration).

Comparison	Incremental QALY[1]	Incremental cost	ICER[2]
Entecavir v lamivudine	0.61	£8179	£13,208[3]
Entecavir v PegINF	0.70	£5307	£7511[3]
Entecavir v telbivudine	0.20	£1421	£6907[3]

[1]QALY, quality-adjusted life year; [2]ICER, incremental cost-effectiveness ratio
[3]The outcome of dividing incremental cost by incremental QALY will produce a result that is different from the reported ICERs due to the rounding effect

Table 4 Base-case results for the manufacturer's economic analysis; lamivudine-refractory disease

Comparison	Incremental QALY[1]	Incremental cost	ICER[2]
Entecavir v adefovir dipivoxil and lamivudine	0.07	-£1002	entecavir dominant
[1]QALY, quality-adjusted life year; [2]ICER, incremental cost-effectiveness ratio			

The results of the probabilistic sensitivity analyses in the MS found that entecavir had the following probabilities of being cost effective if the maximum acceptable amount to pay for an additional QALY gained was £20,000: 57% versus lamivudine, 82% versus peginterferon alfa-2a; and 45% versus telbivudine in HBeAg-positive disease (MS table 6.16). For HBeAg-negative disease the corresponding probabilities were 90%, 100% and 96% respectively (MS table 6.18).

The ERG's sensitivity analyses

The ERG re-ran the sensitivity analysis for HBeAg-positive disease shown in the MS (table 6.14, pages 135–6). The ERG updated the analysis in order to assess which parameters had the most impact on the results when a higher estimate of the level of uncertainty around the drug costs and the utility values was used (+/- 20%, as opposed to +/-5% in the MS).

One-way sensitivity analyses for the comparison between entecavir and lamivudine as first-line antiviral therapy in HBeAg-positive disease in nucleoside-naive patients were performed for a two-year treatment duration (see the ERG report, page 95). The following changes resulted in the ICER increasing to more than £20,000 per QALY gained.

- Changing the transition probability from CHB to compensated cirrhosis from 0.04 (base case) to 0.004 (ICER = £48,797 per QALY gained).
- Changing the transition probability from CHB to HBeAg seroconversion (lamivudine year 1) from 0.18 to 0.24 (ICER = £28,984 per QALY gained).

- Changing the baseline transition probability from CHB to HBeAg seroconversion from 0.09 to 0.06 (ICER = £29,338 per QALY gained).
- Changing the transition probability from CHB to HBeAg seroconversion (entecavir year 1) from 0.18 (base case) to 0.15 (ICER = £21,868 per QALY gained).
- Changing the transition probability from CHB to HBeAg seroconversion (entecavir year 2) from 0.10 to 0.06 (ICER = £21,220 per QALY gained).
- Changing the utility for the CHB HBeAg seroconversion state from 0.97 to 0.73 (ICER = £20,047 per QALY gained).

The ERG re-ran the sensitivity analysis for HBeAg-negative patients shown in the MS (table 6.15, pages 135–136). The ERG updated the analysis in order to assess which parameters had the most impact on the results when a higher estimate of the level of uncertainty around the drug costs and the utility values (+/- 20%, as opposed to +/-5% in the MS) in conjunction with a lifetime treatment duration was used.

One-way sensitivity analyses for the comparison between entecavir and lamivudine as first-line antiviral therapy in HBeAg-negative disease in nucleoside-naive patients were performed for lifetime treatment duration (see the ERG report, page 96). The following changes resulted in the ICER increasing to more than £20,000 per QALY gained.

- Changing the utility estimate for the state ‘response’ from 0.91 (base case) to 0.73 (ICER = £37,779 per QALY gained).
- Changing the transition probability for CHB treatment to compensated cirrhosis (lamivudine year 1) from 0.09 to 0.06 (ICER = £21,504 per QALY gained).
- Changing the transition probability for resistance to compensated cirrhosis: changed from 0.09 to 0.06 (ICER = £20,655 per QALY).

The ERG's scenario analyses

An additional scenario analysis was carried out to explore the effect of changing the assumptions in the manufacturer's models that were not accepted by the ERG. The following changes resulted in the ICER increasing to more than £20,000 per QALY gained.

- Increasing the treatment duration assumption from 2 to 5 years for HBeAg-positive disease increased the ICER from £14,300 to £22,100 per QALY gained. Longer treatment durations gave higher ICERs – £27,100 per QALY gained for 10 years' treatment and £30,300 per QALY gained for 20 years' treatment.
- Assuming that HBeAg-negative disease in people with compensated cirrhosis would be treated for their whole lifetime, and those with compensated cirrhosis receiving treatment would have a similar progression to decompensated cirrhosis, and that this transition probability would be 1.8% for lamivudine, the ICER was £27,124 per QALY gained.
- Making the assumption that 90% of patients start treatment with CHB and 10% of patients start treatment with compensated cirrhosis (rather than 100% starting with CHB), produced an ICER of £42,608 per QALY gained.

3.2 Evidence Review Group comments

The ERG view was that the manufacturer's submission used a reasonable approach to modelling the cost effectiveness of entecavir. From random checking, the models appeared to be accurate.

The duration of treatment assumed in the models was poorly justified. The ERG clinical experts felt that for the majority of patients treatment with the antiviral agents would last longer than the 2 and 5 years assumed in the HBeAg-positive and HBeAg-negative disease models.

The MS provided the lifetime treatment scenario for HBeAg-negative disease, which the ERG clinical experts felt was the most appropriate model. However,

there was uncertainty associated with the paucity of clinical effectiveness data beyond the second year of treatment.

The methods of deriving the year 2 estimates of response to treatment (footnotes to MS, tables 6.4 and 6.5) were not clear but appeared to be based on the assumption of drop-out rates being the same across all treatment groups. This assumption does not seem to be reasonable.

The models' assumption about the clinical practice of excluding patients who progress to the active cirrhotic state from receiving further treatment for CHB was not supported by the ERG clinical experts.

The assumption that all patients present for treatment in the pre-cirrhotic state of disease was not supported by the ERG clinical experts.

The assumption that patients whose disease responds (defined either as seroconversion in the HBeAg-positive disease model or viral suppression in the HBeAg-negative disease model) cannot enter the state of active cirrhosis other than by first entering the state of inactive cirrhosis, differs from those in previously published economic evaluations.

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 the current appraisal relate to this guidance and what is the likely place of entecavir/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

Helen Tucker (Technical Lead) and Janet Robertson (Technical Adviser), with input from the Lead Team (Michael Davies, David Black and Dyfrig Hughes).

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

A The evidence review group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC):

- Shepherd J et al, Entecavir for the treatment of chronic hepatitis B, February 2008

B Submissions or statements from the following organisations:

I Manufacturer/sponsor:

- Bristol-Myers Squibb Pharmaceuticals

II Professional/specialist, patient/carer and other groups

- Association of Clinical Microbiologists
- British Society for Gastroenterology
- Hepatitis B Foundation UK
- Royal College of Pathologists
- Royal College of Physicians

C Additional references used:

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

Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Entecavir for the treatment of chronic hepatitis B

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[redacted]

Conflicts of Interest:

None

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AASLD	American Association for the Study of Liver Diseases
bDNA	Branched-chain deoxyribonucleic acid
BMS	Bristol-Myers Squibb
BNF	British National Formulary
CAS	Chemical Abstracts Service (reference number)
CCRCT	Cochrane Central Register of Controlled Trials
CEA	Cost effectiveness analysis
CEAC	Cost Effectiveness Acceptability Curve
CDSR	Cochrane Database of Systematic Reviews
CHB	Chronic hepatitis B
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DARE	Database of Reviews of Effectiveness
EASL	European Association for the Study of Liver Diseases
ERG	Evidence Review Group
GDP	Gross Domestic Product
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of LIfe
ITT	Intention to treat
LLOQ	Lower limit of quantification
MEIP	Medline in Progress (MEIP)
MEq/mL	Milliequivalents per millilitre
mg	Milligram
MTC	Mixed Treatment Comparison
NA	Nucleotide / nucleoside analogue
NC=F	Analysis method in which non-conformers are analysed as treatment failures
NC=M	Analysis method in which non-conformers are analysed as missing data
NMA	Network meta-analysis
NRR	National Research Register
Peg IFN	Pegylated interferon alpha 2a
PDF	Portable document format
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
qd	Once daily
RCT	Randomised Controlled Trial
QALY	Quality Adjusted Life Year
SD	Standard Deviation
SE	Standard Error
SG	Standard Gamble

SMC	Scottish Medicines Consortium
SMPC	Summary of product characteristics
TRIP	Turning Research into Practice
TTO	Time trade off
ULN	Upper limit of normal
YMDD	Tyrosine methionine aspartate aspartate motif in the catalytic domain of the viral polymerase/reverse transcriptase

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), the licensed indication, and is appropriate to the National Health Service (NHS).

- The population described is adults with chronic hepatitis B (CHB) infection with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. Patient sub-groups include those with HBeAg positive and HBeAg negative CHB; and those who are treatment (nucleoside analogue) naïve or refractory to lamivudine (e.g. those with persistent viraemia and/or genotypical resistance). Patients with co-infections were excluded in accordance with the scope.
- The intervention is entecavir alone in the treatment of CHB.
- Comparators include nucleoside analogues: lamivudine and telbivudine; nucleotide analogue: adefovir dipivoxil, and immune modifiers: interferon alpha 2a and 2b, and pegylated interferon alpha 2a.
- Outcomes include: HBeAg/HBsAg seroconversion rate, virological response (HBV DNA); histological improvement (liver inflammation and fibrosis); biochemical response (e.g. ALT levels); development of viral resistance; and adverse events. Outcomes included in the scope and decision problem but not reported in the submission include time to treatment failure; survival (unless within the context of adverse events) and health related quality of life.

Summary of submitted clinical effectiveness evidence

The manufacturer's systematic review includes five randomised controlled trials (RCTs) all of which compared entecavir with lamivudine:

- Three of the trials were conducted in nucleoside-naïve patients (one in HBeAg positive patients, one in HBeAg negative patients, and one in a mixed HBeAg positive and negative status group).

- The other two were conducted in lamivudine-refractory patients (one in HBeAg positive patients, the other in a mixed HBeAg positive and negative status group).
- Outcome data are reported for up to one year of treatment, and for a sub-set of patients who did not achieve a complete response and who continued treatment in year two. Cumulative proportions of all patients ever attaining treatment response up to two years are also presented. Some of the patients from the RCTs have entered long-term observational extension studies, with treatment continuing up to five years. However, fully published data are not yet available.

The results of the five RCTs showed that:

- After one year of treatment entecavir was statistically superior to lamivudine in terms of the proportion of patients achieving HBV DNA suppression; ALT normalisation; and histological improvement. There was no statistically significant difference between the treatments in the proportion of patients achieving HBeAg seroconversion (HBeAg positive patients only, by definition).
- [redacted] Most of the entecavir-treated patients did not have any detectable resistance-associated substitutions at one year of treatment.
- The proportions of patients with any adverse events or serious adverse events were similar for entecavir and lamivudine. The proportion of patients who withdrew during the first year due to adverse events was similar for entecavir and lamivudine except in one trial where significantly more lamivudine patients withdrew. The number of deaths during treatment was low (<1% in all cases).

The manufacturer also constructed a mixed treatment comparison (MTC) model to compare entecavir with the comparator drugs, in nucleoside-naïve patients. An MTC was not considered possible in lamivudine-refractory patients due to lack of evidence.

- The results of the MTC generally accord with the results of the RCTs, in that entecavir was superior to lamivudine across outcomes, with the exception of HBeAg seroconversion.
- The MTC suggests that entecavir is either significantly better or equivalent to the other comparators, depending on the outcome measure and the time-point.

Summary of submitted cost effectiveness evidence

- The manufacturer's economic evaluation comprises a systematic review of economic evaluations of CHB treatments, and a cost-utility analysis based on a *de novo* economic model.
- Two Markov state-transition models were constructed, one in HBeAg positive patients and one in HBeAg negative patients. The models estimate progression to 14 health states (15 in the HBeAg negative model) representative of progressive CHB related liver disease (e.g. compensated and decompensated cirrhosis; hepatocellular carcinoma). The models have a lifetime horizon and a cycle length of one year.
- In HBeAg positive and negative nucleoside naïve patients, the models compare entecavir with lamivudine, pegylated interferon alpha 2a, and telbivudine. Treatment lasts for two years in HBeAg positive patients, and five years in HBeAg negative patients (with the exception of pegylated interferon alpha 2a which is given for only one year). In HBeAg positive patients who are refractory to lamivudine, entecavir is compared to adefovir added to lamivudine for two years. Response to treatment is defined by HBeAg seroconversion and undetectable HBV DNA.
- In HBeAg positive patients the base case incremental cost-effectiveness ratio (ICER) for entecavir compared to lamivudine was £14,329 per Quality Adjusted Life Year (QALY). Compared to pegylated interferon alpha 2a, the ICER was £8,403 per QALY. Entecavir was associated with the same number of QALYs as telbivudine but at a slightly higher total cost and was therefore dominated. In HBeAg negative patients the base case ICERs were £13,208, £7,511 and £6,907 per QALY, in comparison to lamivudine, pegylated interferon alpha 2a and telbivudine, respectively. In HBeAg positive lamivudine-refractory patients entecavir dominated adefovir added to lamivudine.
- One-way deterministic sensitivity analysis for entecavir compared to lamivudine on all key input parameters, and performed for nucleoside naïve patients, showed that the results were most sensitive to baseline transition probabilities from CHB to (a) seroconversion (spontaneous seroconversion), (b) active cirrhosis, from active cirrhosis to decompensated cirrhosis, baseline cirrhosis risk and treatment effects. ICERs generally remained under £30,000 per QALY.
- Results of the probabilistic sensitivity analysis in nucleoside naïve HBeAg positive patients show that the probability of the ICER for entecavir being below £20,000 per QALY was 57% compared to lamivudine, 82% compared to pegylated interferon alpha 2a, and 45%

compared to telbivudine. In nucleoside naïve HBeAg negative patients the probabilities were 90%, 100% and 96%, respectively.

- The manufacturer included a lifetime treatment scenario in HBeAg negative patients, and the ERG included a scenario of up to 20 years treatment for HBeAg positive patients. The ICERs increased as a consequence, particularly in the latter.

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical- and cost-effectiveness studies of entecavir. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.
- The five entecavir RCTs identified were of generally good methodological quality, and measured a range of outcomes that are appropriate and clinically relevant, although health related quality of life was not reported.
- Overall, the MS presents an unbiased estimate of the efficacy of entecavir versus lamivudine, based on the results of the five RCTs.
- Overall, the manufacturer's economic evaluation accords with the decision problem and the NICE reference case. The approach to modelling was generally considered reasonable and the model was judged to be internally and externally consistent, subject to some uncertainties (see below).
- Disease progression pathways assumed in the economic models are generally consistent with the natural history of CHB, although there were some concerns about some of the structural assumptions (see below).

Weaknesses

- The mixed treatment comparison model (MTC) suffers from certain limitations in conduct and reporting, including: small numbers of studies / single studies in some networks; no assessment or discussion of heterogeneity; and no reporting of criteria for judging statistical significance or equivalence.

Areas of uncertainty

- Given the concerns about the conduct and reporting of the MTC the ERG consider its results to be uncertain. This limits any conclusions that can be drawn regarding the comparative efficacy of entecavir to telbivudine, and to pegylated interferon alpha 2a in nucleoside-naïve patients (NB. notwithstanding the head-to-head RCT evidence comparing entecavir with lamivudine).
- There is relatively limited clinical and cost-effectiveness evidence for entecavir in lamivudine-refractory patients. Head-to-head RCT evidence is available for entecavir versus on-going lamivudine, but only in HBeAg positive patients. Smaller RCTs have been published comparing switching to adefovir versus adding adefovir to on-going lamivudine, but these have not been compared in a statistical indirect comparison to entecavir. The manufacturer only present cost-effectiveness estimates for HBeAg positive, not HBeAg negative, lamivudine-refractory patients.
- Structural assumptions in both the HBeAg positive and HBeAg negative disease models preclude the patients with response from directly entering the active/compensated cirrhosis health state. The rationale for this assumption was not clear and it is not possible to estimate the impact of these structural assumptions.
- Treatment of CHB in many patients will be longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models, respectively. However, there a paucity of published clinical effectiveness data from RCTs beyond the second year of treatment (NB. long-term observational studies (up to five years) are in progress). Increasing the treatment duration in scenario analysis results in higher ICERs.
- No data are presented in the submission of the efficacy and safety of entecavir in combination with other licensed agents.
- Contrary to the assumptions in the manufacturer's economic evaluation, a certain proportion of CHB patients will first present with compensated cirrhosis. Moreover, it is unlikely that the treatment is terminated once the patients progress to the active cirrhosis stage of disease. Changing these assumptions to reflect a more realistic scenario increased the ICER for entecavir compared to lamivudine.

Key issues

The validity and reliability of results of the cost-effectiveness analysis are likely to be affected by the following:

- The uncertain effect of the modelling assumption of patients with response transitioning exclusively to the inactive cirrhosis state;

- The assumed duration of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively does not reflect clinical practice.
- The exclusion of patients who progress to the active cirrhosis state from receiving treatment for CHB;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease;

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Bristol Myers Squibb on the clinical effectiveness and cost effectiveness of entecavir for chronic hepatitis B (CHB). It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 12th December 2008. A response from the manufacturer via NICE was received by the ERG on 24th December 2008 and this has been included as an Addendum in this report (Appendix 1). Annotations referring to the Addendum occur throughout the ERG report where applicable.

The ERG noted that labelling of tables and sections in the MS is inconsistent:

- Tables on MS pages 32-34, 44-46, 47-51, 57-59, 60-62, 63-65, 94, 95 and 96 have no number or caption but are immediately preceded by section numbers which help to identify them. Where necessary these tables are cited in the ERG report by their section and page numbers.
- Tables on MS pages 67, 68, 71, 72, 74, 75, 77, 78, 80, 90 have no numbers or captions and are not preceded by section headings. Where necessary these tables are cited in the ERG report by their page numbers.
- The order of tables in relation to sections is somewhat confusing, with Tables 5.1 to 5.4 (pages 36-41) preceding Tables in section 5.3 (pages 44-65). This makes some tables less easy to find in the MS but does not affect cross-referencing or interpretation of data.
- Table 5.3 (MS page 41) is incorrectly labelled Table 5.1.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer has provided a reasonably comprehensive overview of the condition. A distinction between HBeAg positive and HBeAg negative forms of the disease is provided, although differences in disease progression between the two is not discussed. The specific phases of the disease are not mentioned (e.g. the immune tolerant phase; the

immunoactive/immune clearance phase; the inactive carrier/immune control phase and the immune escape phase). Treatment is indicated in the immunoactive/immune clearance phase and if successful leads to inactive carrier status, although reactivation can occur at the immune escape phase[1]. It would have been helpful to mention these phases as it puts the rest of the submission, particularly the economic model, into context.

The manufacturer reports that there are around 180,000 people infected with CHB in the UK , based on 2004 prevalence figures reported by the British Liver Trust. If only England and Wales are considered then the prevalence is around 156,000. The Hepatitis B Foundation recently estimated that the prevalence of CHB in the UK has increased to 325,000 (not mentioned in the MS) and is thought likely to increase further as a consequence of increasing rates of immigration of people from countries with a high CHB prevalence[2].

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides a clear and generally accurate overview of current service provision. Recently published clinical guidelines are described, such as those produced by the American Association for the Study of the Liver. It is noted that European guidelines were published in 2003, but are now out of date. There are currently no UK clinical guidelines, although NICE's 2006 guidance on the use of pegylated interferon alpha and adefovir dipivoxil is described. No other UK relevant guidelines are known to the ERG.

It is noted that, based on market research, only a small selected group of patients in the UK begin treatment with an interferon (<10%, of which >85% use pegylated interferon alpha), of which around a third will undergo HBeAg seroconversion and enter the inactive carrier stage of infection. It is suggested that the role of interferon is less clear in HBeAg negative patients who, by definition, cannot seroconvert. In such patients initiation of therapy with a nucleoside analogue is the most likely option. Expert clinical opinion sought by the ERG confirms this, with a circumscribed course of interferon primarily aiming to induce seroconversion via an immuno-modulatory response. Nucleoside analogues, in contrast, aim to induce viral suppression and are therefore more suited to longer-term therapy in patients in whom HBeAg seroconversion is less likely/not possible. Interferon is therefore used as a first line therapy primarily for HBeAg positive CHB patients with compensated liver disease, although some HBeAg negative patients will also receive it.

The manufacturer states that lamivudine is the most commonly used treatment in nucleoside-naïve CHB patients in the UK, with the addition of adefovir as rescue therapy upon emergence of viral resistance. This is based on market research data (cited as data on file). It suggests that only a minimal amount of evidence exists to support the use of adefovir as a rescue treatment in lamivudine resistance. This appears a reasonable assertion as the pivotal trials of adefovir were conducted in largely nucleoside-naïve patients.[3,4] However, the manufacturer could have cited the two RCTs evaluating adefovir rescue treatment [5,6] that were included in the assessment that underpinned NICE's guidance[7]. These trials are not cited in relation to the manufacturer's assertion, although they are reported in a later section for purposes of an indirect comparison in lamivudine-refractory patients (section 5.6.5 of the MS).

The manufacturer suggests that there is a degree of uncertainty regarding current best practice particularly in relation to choice of drug, and viral resistance (MS, page 30). It is noted that there is a lack of consensus around treatment pathways, and clinical experts consulted by the ERG agree with this to some extent. Aside from the 12 specialist centres around the UK, the majority of patients will be treated in District General Hospitals by gastroenterologists who have limited training in Hepatology.

A comparison of the international clinical guidelines is presented in a table (MS section 4.6). In all guidelines presented entecavir is one of the recommended first line treatments.

The MS suggests that there is no consensus around the optimal treatment duration in HBeAg negative patients (p. 24). Clinical experts consulted by the ERG reported that, in practice, the majority of these patients will receive life-long treatment. Thomas (2007), in a review of international clinical guidelines on the management of CHB, suggests that the effectiveness of treatment discontinuation should be subjected to further evaluation[1].

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem is adults with CHB infection with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine

aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This matches the scope for the appraisal, the licensed indication, and is appropriate for the NHS. However, the scope and the decision problem do not include patients with advanced (decompensated) liver disease, including pre and post liver transplant patients. Therefore, the submission (and the appraisal) will not be relevant for this patient group. The scope and the decision problem also do not include patients who are co-infected with human immuno-deficiency virus (HIV) or hepatitis C (HCV) or D (HDV). The decision problem distinguishes between sub-groups of patients, in accordance with the scope, namely HBeAg positive and negative patients, and treatment naïve patients and treatment (nucleoside analogue) resistant patients.

2.3.2 Intervention

The intervention described in the decision problem is entecavir alone in the treatment of CHB. This reflects the licensed indication and is appropriate for the NHS. However, the scope specified that the intervention could be entecavir alone or in combination with other therapies. No mention is made of combination therapies in the decision problem. It is not clear whether the absence of mention of combination therapy in the licensed indication prohibits such use. It is also of note that none of the randomised controlled trials (RCTs) of entecavir identified by the manufacturer has evaluated its use in combination with other drugs.

The MS states that the optimal duration of treatment is unknown and cites the summary of product characteristics (SPC)[8] which provides guidance on when to discontinue treatment. In HBeAg positive patients treatment should be continued until HBeAg seroconversion or until HBsAg seroconversion, or if there is evidence of loss of efficacy. In HBeAg negative patients treatment should be continued until HBs seroconversion or if there is loss of efficacy. Patients on long-term therapy (> 2 years) should be reassessed regularly to determine whether that particular treatment is still appropriate.

Expert clinical opinion suggests that entecavir is currently used in some parts of England and Wales, although generally not as a first line treatment. Clinical opinion also suggests that for those who have failed to respond to, or who have relapsed, following interferon or pegylated interferon alpha, it would be advantageous to proceed directly to a combination of entecavir and another nucleoside / nucleotide analogue. It is thought that this would lessen the risk of cross-

resistance, a problem associated with the sequential use of nucleoside / nucleotide analogue monotherapies. This is also a problem that has been experienced in the HIV/AIDS and tuberculosis fields, where combination therapies are now commonplace.

2.3.3 Comparators

The comparators listed in the decision problem reflect those in the scope of the appraisal and are all appropriate to the NHS. These include pegylated and non-pegylated interferon alpha-2a, lamivudine, telbivudine, and adefovir dipivoxil. The MS presents head-to-head RCT data for entecavir compared with lamivudine, and indirect evidence via network meta-analysis for entecavir compared with telbivudine and pegylated interferon alpha-2a.

2.3.4 Outcomes

The comparators listed in the decision problem reflect those in the scope of the appraisal and are all appropriate to current clinical practice. These include viral response (HBV DNA); HBeAg loss and seroconversion (only in patients who are HBeAg positive, by definition); HBsAg loss and seroconversion; biochemical response (ALT - alanine amino transferase); development of viral resistance; histological improvement; health related quality of life (HRQoL); adverse events and survival. There do not appear to be any other clinically meaningful outcomes that have not been included.

Although not generally a primary outcome in the pivotal RCTs presented by the MS (see Section 3.1.4), the MS provides a rationale for why viral suppression should be considered as the key marker of treatment effect in their background section on CHB (MS section 4.5.1, page 28). Results of a large population based cohort study in Taiwan (the REVEAL study[9]) are cited as supporting the association between baseline viral load and the development of cirrhosis, hepatocellular carcinoma (HCC) and mortality. It is asserted that there are uncertainties around the appropriateness of other markers of treatment effect, namely ALT, histological improvement and HBeAg seroconversion. Expert clinical opinion agrees that viral suppression is a clinically meaningful treatment outcome, particularly in patients in whom HBeAg seroconversion is unlikely to occur (e.g. HBeAg positive patients who have not seroconverted or who have relapsed following earlier treatment, such as interferon alpha or pegylated interferon alpha), or in whom it is not applicable (e.g. HBeAg negative patients).

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

3.1.1 Description of manufacturer's search strategy

The manufacturer has provided a reasonably detailed description of its search strategies. However the ERG had to request clarification from the manufacturer on certain details, as outlined below.

3.1.1.1 Clinical effectiveness searches

The search process described was used to inform both the assessment of clinical effectiveness (section 5.1 of the MS) and the mixed treatment comparison (MTC) (section 5.6 of the MS).

The manufacturer has replicated the search strategies used by SHTAC in the previous assessment report on adefovir and pegylated interferon alpha 2a[7] which underpinned NICE's existing guidance (NICE Technology Appraisal 96). The manufacturer states that the full range of databases used by SHTAC were not searched for the submission due to difficulties in access. The minimum database search criteria specified by NICE were searched by the manufacturer (i.e. Medline, Embase, Medline in Progress (MEIP) and Cochrane). In addition, two of the Centre for Reviews and Dissemination (CRD) databases were also searched (DARE; HTA database). The host system used for the electronic bibliographic searching was not reported in the submission. The ERG requested clarification and the manufacturer reported that Dialog Datastar was used to search Embase, and that Ovid and Dialog Datastar had been used to search Medline (see Appendix 1, A4 and A5).

The SHTAC strategy was extended by the manufacturer to incorporate entecavir, telbivudine, and lamivudine. The searches were limited to articles published in the English language. No time limits were applied to the clinical effectiveness searches, but the ERG requested clarification about the search dates of the various electronic bibliographic databases, as these vary according to which host system is used. The manufacturer responded with the information

for each database (see Appendix 1, page 1). Each database was searched from its inception, up to approximately 21st September 2007.

The search strategy, as adapted for each bibliographic database, was not presented in the submission. However, the strategy for Medline, Embase and the Cochrane Library was supplied on request to the ERG (see Appendix 1, pages 10 to 13). The strategy contains a mixture of free text and index terms, although for the Embase search it is not explicit whether index terms were used. It is not clear from the search example given by the manufacturer if all the component databases of the Cochrane Library were searched or if the Cochrane Database of Systematic Reviews (CDSR) alone was used. The ERG noticed what appeared to be a few errors with the syntax used in the strategy and requested clarification from the manufacturer. The manufacturer confirmed that these were typographical errors in the submission, rather than errors in the strategies themselves (see Appendix 1, pages 2 and 3). The strategies appear to be comprehensive although only the generic names of the drugs were included in the strategy, rather than including trade names and CAS registry numbers or applying field tags to search for these. It is not considered, however, that using these would have produced any additional references.

The ERG also enquired whether the number of hits generated from each database could be supplied. The manufacturer reported that this information had not been saved by the agency who conducted the searching. Without this information it is not possible to reproduce the search strategies and compare search results.

The manufacturer also ran a 'simple search strategy' specifically to identify articles relating to entecavir. This was a bibliographic reference chasing exercise to check for any missed trials. It is stated that this strategy was also run for telbivudine (MS Appendix 8.3.1, page 1), although terms for this drug are not presented in the actual strategy itself (MS Appendix 8.3.1, page 18). There is no explanation of why the other comparator drugs were not subjected to the simple search approach. This is particularly important given that the other drugs were included in the MTC.

In terms of on-going trials the manufacturer reports searching clinicaltrials.gov (http://clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com), as well as internal company databases. The National Research Register (NRR) is not reported as having

been searched, although this is not a NICE pre-requisite (NB. At the end of 2007 the NRR has been decommissioned and is now available as an archive only). Conference proceedings have not been reported as individually searched, although the Cochrane Central Register of Controlled Trials (CCRCT) has been searched and this does include hand-searched conference proceedings.

In summary, the search process for clinical effectiveness studies reported by the manufacturer is generally comprehensive, with key databases searched using a combination of free-text and index terms. The search strategy is not, however, fully reproducible due to limitations in reporting.

3.1.1.2 Cost effectiveness searches

The cost-effectiveness searches have satisfied most of the minimum database criteria set by NICE (namely, Medline, Embase, and MEIP). The manufacturer has exceeded the criteria by searching internal company databases, The Cochrane Library, the HTA databases, the TRIP database (Turning Research into Practice), and websites of organisations including NICE, The Scottish Medicines Consortium (SMC), The European Association for the Study of Liver Diseases (EASL), The American Association for the Study of Liver Diseases (AASLD), as well as a Google internet search. It is not explicitly stated whether the NHS Economic Evaluation database (NHS EED) was searched, but it is assumed it was accessed via the CRD databases which was were mentioned by the manufacturer as having been searched. It is not stated whether the Health Economic Evaluation Database (HEED), one of NICE's database criteria, was searched.

The date of the searches is recorded as "during September 5th and October 10th 2007".(MS page 101). The host system used for Embase and Medline is reported as www.embase.com. It is stated that no time limits were applied, so presumably all databases were searched back to their inception.

It is reported that all search terms were mapped to EMTREE terms and exploded, as well as included as free-text terms (MS, section 8.5.4). However, the strategy is not reproducible as the mapped terms are not recorded. It would have been preferable to record the exact search

strategy that included the free text terms and subject headings, so that it could be reproduced, or at least have clearly defined which terms were free text and which were index terms.

The search strategy is not entirely transparent and therefore not easily reproducible because the list of free text terms is given, but they have not necessarily recorded the mapped index terms (MS section 8.5.4 "All search terms were mapped to EMTREE terms and exploded as well as included in a free text term"). The range of free-text terms looks sensible but there is no overt truncation of free text terms, although it is thought that the Datastar Dialog platform can be programmed to identify plurals and variations of endings of words. There is no indication in the search strategy as to which fields have been searched (title, abstract, subject headings etc.). However, it does say that the mapped headings have been exploded.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Three different sets of inclusion criteria are presented in the MS, all of which were applied to the same set of search results.

- The first set is for the clinical effectiveness systematic review of entecavir studies presented in section 5.2.2 of the MS. This is the focus of the clinical effectiveness evidence for entecavir in the submission.
- The second set was for studies screened for possible inclusion in the MTC, and is presented in Appendix 8.4.
- The third set relates to a 'systematic review of licensed therapies for chronic hepatitis B', which incorporates adefovir, pegylated interferon alpha 2a, lamivudine, telbivudine and entecavir, presented in Appendix 8.3 of the MS.

Although these sets of criteria are generally similar there are some differences, and these are highlighted below.

Inclusion criteria for systematic review of entecavir (MS section 5.2.2)

The criteria are appropriate to the decision problem and the licensed indication. Trials were only included if one of the arms evaluated entecavir as a single agent. As mentioned earlier in section 2.3.2, the scope of the appraisal also permitted entecavir in combination with other

agents. It is not clear whether any trials of entecavir combination therapy have been conducted and published. Eligible comparators were lamivudine, telbivudine, and pegylated interferon alpha 2a in nucleoside-naïve patients, and the combination of adefovir and lamivudine in patients who were resistant to lamivudine. It is presumed that interferon alpha is not included as this drug has now been superseded by pegylated interferon alpha.

Note that the scope for the appraisal does not specify which patient sub-group the comparators have to be have been evaluated in (i.e. nucleoside-naïve or resistant to lamivudine). Consequently adefovir, in theory, could be the comparator in the treatment of nucleoside-naïve patients, despite current NICE guidance which specifies that it should not normally be given before treatment with lamivudine. However, the manufacturer's inclusion criteria accord with the guidance, in that trials in which adefovir is a comparator cannot be included unless it has been added to lamivudine in patients who are lamivudine resistant. As will be commented upon later, at least one RCT of adefovir in nucleoside-naïve patients appears to have been excluded on this basis (although it was included in the MTC in order to complete the data network - see section 3.1.2.1). Although placebo or standard care/no treatment trials were eligible they were to be excluded if active comparator trials were identified (NB. All five trials that were included compared entecavir with lamivudine – see section 3.3.1).

Eligible patients were adults with compensated liver disease and active CHB, either HBeAg positive or negative, and either nucleoside-naïve or lamivudine-refractory. Studies of patients with decompensated CHB liver disease were excluded, as were those which evaluated treatment of post-transplant patients, in accordance with the licensed indication. Studies of co-infected patients (e.g. with HIV) were also ineligible, in accordance with the scope and decision problem. Studies less than 48 weeks of duration were excluded, as it was considered that shorter studies would not capture end-points such as HBeAg seroconversion. This criterion was not mentioned in the scope or decision problem (although note that the QUOROM flowchart on page 42 of the MS shows that two of the entecavir studies screened were excluded on the basis of inadequate duration. From examination of the list of excluded studies in MS Appendix 8.3 it appears one was a 28 day study, whilst the other treated patients for 24 weeks).

Only fully published RCTs were eligible (see section 3.1.2.1), however, observational extension studies were permitted (these are reported in a separate section on 'Non-RCT evidence', MS page 92). All other observational studies were excluded. Studies published in abstract form

were excluded, and unpublished studies conducted by the manufacturer were only included where a clinical study report was available. Reviews were only analysed for bibliographic checking. Non-English language articles were excluded.

It is not stated whether screening was conducted independently by more than one person. However, independent screening was conducted for the systematic review of licensed therapies (see below, and MS Appendix 8.3, page 1) it is therefore presumed that a similar approach was used here.

Inclusion criteria for mixed treatment comparison (MTC) (MS section 5.5)

The MTC is presented in MS section 5.5, with further detail of the inclusion/exclusion criteria provided in MS Appendix 8.4.

- The relevant interventions were entecavir (0.5mg), lamivudine (100mg), pegylated interferon alpha 2a (180mg), and telbivudine (600mg). Studies had to include at least two interventions included in the scope of the project or form part of a network of evidence, thus permitting inclusion of placebo and adefovir.
- In terms of patient characteristics the criteria were similar to the other sets of criteria, in that only patients with compensated CHB liver disease were eligible, and transplant patients and those co-infected were ineligible.
- Only RCTs were eligible, whilst conference abstracts were excluded (unless derived from a published RCT). Although not stated in the criteria, clinical study reports held by the manufacturer were included (as evident from the flow diagram in MS appendix 8.4, page 9).
- Results from studies were only included if the HBeAg status of the patient population for a reported end-point was stated or could be inferred. It is stated that studies must report at least one of the required outcome measures at either one or three years. It is not clear why these time points were chosen (as opposed to year one or two), and no list of outcomes is specified although it is presumed that the list of outcomes in the decision problem was used.

A QUOROM flow chart is presented showing the inclusion / exclusion of studies at different stages of the review process (MS Appendix 8.4.2, page 9). The starting point is the 110 studies identified through the systematic review of entecavir for CHB (see above). (NB. The ERG queried whether this figure should be 109, and the manufacturer clarified that the figure 110 was a typographical error – see Appendix 1, A19). A further seven clinical study reports were also

added. Application of the criteria resulted in 21 RCTs being included in the MTC (NB. The ERG queried this with the manufacturer, and believe the actual figure to be 19, see section 3.1.2.1). The ERG has not independently checked to assess whether all of the RCTs appear to meet the inclusion criteria set by the manufacturer.

A breakdown of the number of studies excluded by reason is given (91 articles and 2 clinical study reports, see MS Appendix 8.4.2, page 9), but a bibliographical listing of each study together with the reason for exclusion was not included. The ERG requested such a listing but the manufacturer replied that this was not feasible within the timeframe (see Appendix 1, A6). The biggest proportion of exclusions was due to study design not being an RCT (n=42).

Inclusion criteria for systematic review of licensed therapies for chronic hepatitis B (MS Appendix 8.3)

Appendix 8.3 of the MS reports a slightly different set of inclusion / exclusion criteria for the systematic review of all licensed therapies for CHB. This was undertaken to enable the manufacturer to replicate the search strategy used by SHTAC in the previous assessment report for NICE on pegylated interferon alpha 2a and adefovir[7]. The strategy was extended to include entecavir, telbivudine and lamivudine, the purpose being to 'identify relevant reports for the purpose of further narrative review and possible meta-analysis' (MS Appendix 8.3, page 1). It should be noted that, with the exception of the studies also included in the systematic review of entecavir and in the MTC, none of the studies are reported to have been subjected to data extraction, appraisal or synthesis.

The criteria are similar to those specified for the systematic review of entecavir above. However,

- There is no specification as to whether entecavir (or any of the other drugs) may be used as single or combined agents, and no comparators are stated.
- In terms of study design it is stated that comparative studies and non-comparative studies with long term follow-up (greater than or equal to one year) were included. The systematic review of entecavir, as well as the MTC, restricted inclusion to RCTs in accordance with the decision problem and the scope.
- The criteria specify that both pegylated interferon 2a and 2b are eligible, when the latter is not currently licensed in the UK and is not included in the scope of the appraisal or the previous NICE appraisal of CHB. Of the 15 pegylated interferon alpha studies meeting the

inclusion criteria, at least nine evaluated pegylated interferon alpha 2b (MS Appendix 8.3, page 8). However, none of the 15 studies are actually analysed in the submission, except for two studies of pegylated interferon alpha 2a which were included in the MTC (see above). Therefore, inclusion of studies of this unlicensed drug does not appear to influence the results presented in the submission.

- It is also stated that pharmacokinetic and in vitro studies were ineligible, which was not stated in the inclusion criteria for the systematic review of entecavir, discussed above.

It is reported that 1009 'potentially useful reports' were screened on title and abstract (MS Appendix 8.3, page 2) which is the same number specified in the QUOROM flow diagram in the systematic review of entecavir (MS section 5.2.6). Of these a total of 18 entecavir studies were selected for further screening. (NB There is a discrepancy between the number of entecavir articles selected for further screening in MS section 5.2.6 and in Appendix 8.3. In the former the number specified is 18, whilst in the latter it is stated as 14 (see page 3). The ERG queried this with the manufacturer who reported that this is a typographical error and the correct figure is 18 – see Appendix 1, A16).

It is stated that titles and abstracts were screened by one reviewer, and these were checked by two other reviewers with differences resolved through discussion.

Application of these criteria resulted in 109 RCTs being included in the systematic review of licensed therapies for CHB (63 lamivudine; 15 pegylated interferon alpha; 19 adefovir; 10 entecavir and 2 telbivudine). The ERG has not independently checked to assess whether all of these appear to meet the inclusion criteria set by the manufacturer. As mentioned above, not all of these studies were actually analysed in the submission. A sub-set of five entecavir studies were included in the systematic review of entecavir (MS section 5.2.2), and a subset of 19 studies were included in the MTC (see above). A bibliography of the remaining studies is presented, but with no further detail on their characteristics or results (MS Appendix 8.3, pages 8 to 13).

A breakdown of the number of studies excluded by reason is given (MS Appendix 8.3, page 3), but a bibliographical listing of each study together with the reason for its exclusion was not included. The ERG requested such a listing but the manufacturer replied that this was not feasible within the timeframe (Appendix 1, page 3).

Inclusion criteria - summary

The manufacturer has presented three sets of inclusion criteria for application to the same set of search results. Although generally similar they are reported in slightly different ways and used for different purposes. The reporting is slightly confusing and would have benefited from a more unified inclusion/exclusion strategy reported in a more consistent manner. Nonetheless, the criteria appear to generally reflect the decision problem and the scope of the appraisal.

3.1.2.1 Identified studies

The clinical evidence section of the MS (section 5) begins with a table headed as a 'Complete list' of 12 entecavir studies. It should be noted that only a sub-set of five of these studies met the manufacturer's inclusion criteria for the systematic review. It is presumed the remainder are presented for completeness. This report will therefore focus on these five RCTs, all of which compared entecavir with lamviudine:

- **Study 014** (Chang *et al*, 2005;[10] CSR[11]). HBeAg positive and negative patients with recurrent viraemia on lamivudine. Dose ranging multi-national phase II trial.
- **Study 022** (Chang *et al*, 2006;[12] CSR[13]). HBeAg positive nucleoside-naïve patients. Multi-national phase III RCT.
- **Study 023** (Yao *et al*, 2007;[14] CSR). HBeAg positive and negative Chinese patients. Phase III RCT conducted in China.
- **Study 026** (Sherman *et al,* 2006;[15] CSR[16]). HBeAg positive lamivudine-refractory patients. Multi-national phase III RCT.
- **Study 027** (Lai *et al*, 2006;[17] CSR[18]). HBeAg negative nucleoside-naïve patients. Phase III RCT. Multi-national phase III RCT.

Studies 022 and 027 were very similar in design and patient characteristics, the key distinction between them being that the former restricted inclusion to patients with HBeAg positive CHB, whilst the latter included HBeAg negative patients. Both aimed to assess the non-inferiority and thence the superiority of entecavir compared to lamivudine. Duration of treatment was 52 weeks at which time "complete virological responders", defined as having undetectable HBV DNA by branched-chain (bDNA) assay and undetectable HBeAg (Study 022) or ALT <1.25 x the upper

limit of normal (ULN) at week 48 (Study 027), discontinued and were followed for 24 weeks. "Partial virologic responders", defined as having undetectable HBV DNA by bDNA assay and detectable HBeAg (Study 022) or ALT of at least 1.25 x ULN (Study 027), continued therapy up to week 96, or until complete virological response was achieved (Study 022). In both studies "non-responders", defined as having detectable HBV DNA by bDNA at week 48, discontinued treatment at week 52. Patients from studies 022 and 027 have been entered into an open-label long-term extension study (Study 901[19]) in which patients will be treated for up to five years (MS, page 41, Table 5.4). (See also section 3.1.2.3 of this report).

Study 023 was also similar in design to 022 and 027, but a key distinction was that it was conducted entirely within China with a mixed population of HBeAg positive and negative patients. In common with Studies 022 and 027, patients could progress to a second year of treatment according to their response at week 48. Those achieving a "consolidated response", defined as HBV DNA <0.7 milliequivalents per millilitre (ME q/ml) by bDNA assay and HBeAg negative for at least 24 weeks (weeks 24–48) and ALT <1.25 × ULN at week 48, stopped treatment at week 52 and were followed up for 24 weeks. Those exhibiting a partial response, defined as HBV DNA <0.7 MEq/mL by bDNA but not yet meeting criteria for consolidated response at week 48, continued treatment. Virological non-responders at week 48 (HBV DNA ≥0.7 MEq/mL by bDNA) discontinued at week 52. The CONSORT flow chart for this study states that 69 patients have entered the A1463-050 open-label extension study (MS section 5.3.3.3).

Study 026 was designed to test the superiority of switching to entecavir compared to continuing with lamivudine in HBeAg positive patients who had become refractory to lamivudine. Refractory was defined as any of the following:

- Persistently detectable HBV DNA by bDNA assay after at least 36 weeks lamivudine treatment
- Recurrence of detectable HBV DNA by bDNA assay on two determinations after achieving undetectable HBV DNA (by bDNA assay) on lamivudine
- Recurrence and persistence of HBV replication after discontinuing lamivudine provided that lamivudine had been reintroduced and maintained for ≥12 weeks prior to screening; or documented YMDD mutation and HBV viraemia on lamivudine regardless of duration of therapy.

The same protocol used in Study 022 applied in this study with regard to whether or not patients progressed to treatment in year two.

Study 014 was an earlier phase II RCT designed to test the efficacy and safety of three different doses of entecavir with the aim of selecting an optimal dose for further study in phase III clinical trials. Eligible patients were viraemia after at least 24 weeks of lamivudine therapy or had documented lamivudine resistance.

- Patients who achieved a virological response at week 24, defined as ≥1 $\log_{10}$ reduction in HBV DNA by bDNA assay from baseline, continued treatment to week 52.
- Patients with 'minimal' virological response (<1 $\log_{10}$ reduction in HBV DNA and ≥ 10 MEq/mL by bDNA assay at week 24) discontinued treatment and either started alternative HBV therapy or were enrolled into a rollover study of entecavir plus lamivudine combination therapy (Study AI463-901).
- Patients who achieved a "complete response" at week 48 (HBV DNA < lower limit of quantification (LLOQ) by bDNA assay, loss of HBeAg and normal ALT for HBeAg positive patients at baseline; HBV DNA < LLOQ by bDNA assay, maintenance of negative HBeAg and normal ALT for HBeAg negative patients at baseline) discontinued study therapy and were followed for up to 24 weeks.
- Patients who demonstrated a "partial response" at week 48 (HBV DNA < LLOQ by bDNA but positive for HBeAg or abnormal ALT) continued treatment for an additional 24 weeks (total of 76 weeks) or until they were enrolled into the open-label phase of this study.
- Patients who did not demonstrate response at week 48 (HBV DNA ≥ LLOQ by bDNA assay) discontinued treatment. These non-responders and subjects who had a relapse off treatment (HBV DNA ≥LLOQ by bDNA assay, or HBeAg positive, or ALT >1.5×ULN on two determinations at least 2 weeks apart after achieving complete response) could either enrol in Study AI463-901 (Study 901[19]) or start alternative anti-HBV therapy.

All five RCTs were published in academic journals and portable document format (PDF) versions of these were supplied by the manufacturer. The manufacturer also supplied clinical study reports (CSRs) for each trial in PDF form. These reports total over 1000 pages long in many cases and the ERG have not systematically assessed them in great detail.

Although the ERG has not checked every detail, the information presented in the MS systematic review seems to be representative of the information in the published journal articles (see

section 3.3.1). The CSRs contain additional information not present in the published trial reports. For example, they report outcomes for the cohort of patients who continued treatment into year two, as well as cumulative outcome data for all for all treated patients at the end of year two. The published trial reports, in contrast, only report outcomes at the end of one year of treatment (up to 48 weeks). Outcomes at year two are reported in the clinical evidence section of the MS (section 5.5) for four of the RCTs included in the manufacturer's systematic review, and are also included in the MTC. As these data have not been published in an academic journal they will not have been subjected to external peer review.

The five RCTs are described in further detail in MS section 5.3, with separate tables reporting:

- The methods used (e.g. the regimen and trial protocol; study phase; randomisation methods - see MS Table 5.3.1).
- The characteristics of the participants (e.g. trial inclusion/exclusion criteria; baseline characteristics - see MS Table 5.3.2), and the numbers of patients (e.g. number enrolled; number randomised; number treated; number who discontinued – see MS section 5.3.3). (In addition a CONSORT flow chart is provided for each of the five included RCTs showing the number of patients enrolled, the number randomised to study groups, and the number completing the various phases of the trials).
- Trial outcomes (e.g. primary and secondary outcome measures; and evidence to support the validity of the measures – with some unnecessary repetition throughout the table - see MS Table 5.3.4)).
- Statistical analyses and definitions of study groups (e.g. hypotheses; statistical tests used; sample sizes and power calculations; study withdrawal / intention to treat procedures).

The process undertaken by the manufacturer for the extraction of data from the included trials is not detailed in the MS (e.g. whether it was performed by one person and checked by a second).

An overview of the five included RCTs is provided in Table 5.2 (MS page 40). Their characteristics are summarised below in Table 1.

Table 1 Characteristics of the included entecavir RCTs

Reference	Methods	Participants	Outcomes
Study 014 (Chang *et al*, 2005[10]) (CSR[11])	*Design:* phase II, multicentre international double-blind, RCT *Interventions:* 1) entecavir 0.1mg qd 2) entecavir 0.5mg qd 3) entecavir 1mg qd 4) lamivudine 100mg qd *Duration:* 52 weeks (patients with virological response at week 24 continued treatment to week 52)	Aged ≥16 years with HBeAg negative or positive compensated CHB, lamivudine-refractory *Numbers:* 1) 47 2) 47 3) 42 4) 45 NB. Outcome data are only presented for groups 3 and 4 in the submission	*Primary:* • Proportion of patients with undetectable HBV DNA (by bDNA assay) at week 24. *Secondary:* • Proportion of patients with undetectable HBV DNA (by bDNA assay) at week 24. • Proportion of patients with undetectable HBV DNA (by PCR assay) at week 24 and week 48 • Mean reduction in HBV DNA • Proportion of HBeAg positive patients at baseline who lost HBeAg by week 48 • Proportion of HBeAg positive patients at baseline who seroconverted by week 48 • Proportion of patients with abnormal ALT at baseline who normalised at weeks 24 and 48.
Study 022 Chang *et al,* 2006[12]) (CSR[13])	*Design:* phase III, multicentre double-blind international, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (partial virologic responders continued until 96 weeks or until complete virologic response achieved)	Aged ≥16 years with HBeAg positive compensated CHB, treatment naïve *Numbers:* 1) 354 2) 355	*Primary:* • Proportion of patients with histological improvement at week 48 *Secondary (at week 48):* • Reduction in HBV DNA from baseline • Proportion of patients with undetectable HBV DNA (on PCR assay) • Decrease in Ishak fibrosis score • HBeAg loss; HBeAg seroconversion • Normalisation of ALT • Safety
Study 023 (Yao *et al*, 2007[14]) (CSR[20])	*Design:* phase III, multicentre double-blind Chinese, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with partial response at week 48 but not a consolidated response continued to week 96)	Aged ≥16 years with HBeAg negative or positive compensated CHB, treatment naïve *Numbers:* 1) 258 2) 261	*Primary:* • Composite end-point – proportion of patients with both HBV DNA (on bDNA assay) and ALT response at week 48 *Secondary (at week 48):* • Mean reduction in HBV DNA (by PCR assay) • HBV DNA response (PCR assay) • HBeAg loss; HBeAg seroconversion • ALT normalisation

			• Safety
Study 026 (Sherman *et al,* 2006[15]) (CSR)[16]	*Design:* phase III, multicentre international double-blind, RCT *Interventions:* 1) entecavir 1mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with partial response at week 48 but not a consolidated response continued to week 96)	Aged ≥16 years with HBeAg positive compensated CHB, lamivudine-refractory *Numbers:* 1) 141 2) 145	*Two co-primary end-points (at week 48):* • Histological improvement • Composite end-point – proportion of patients with both HBV DNA (on bDNA assay) and ALT response *Secondary (at week 48):* • HBV DNA response (by PCR assay) • Mean change in serum HBV DNA • Decrease in Ishak fibrosis score • HBeAg loss; HBeAg seroconversion • Normalisation of ALT • Safety analysis
Study 027 (Lai *et al*, 2006[17]) (CSR[18])	*Design:* phase III, multicentre double-blind international, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with virologic response only continued until 96 weeks.	Aged ≥16 years with HBeAg negative compensated CHB, treatment naïve *Numbers:* 1) 325 2) 313	*Primary:* • Proportion of patients with histological improvement at week 48 *Secondary (at week 48):* • Reduction in HBV DNA from baseline • Proportion of patients with undetectable HBV DNA (on PCR) • Decrease in Ishak fibrosis score • Normalisation of ALT • Safety

Mixed treatment comparison (MTC)

Most of the detail of the characteristics of studies included in the MTC are provided in Appendix 8.4 of the MS. The manufacturer states that 24 studies were included in the network meta-analysis (MS Appendix 8.4 page 2). However:

- The ERG suspected this figure included multiple publications for the same trials, and queried this with the manufacturer who clarified that there were 24 reports describing 21 studies (see Appendix 1, page 6).
- On further inspection it appears that there are three publications describing the pivotal GLOBE trial of telbivudine compared to lamivudine (reference numbers 9, 14, and 16 in the bibliography in Appendix 8.4, p.24-25).
- The ERG therefore estimates the number of studies included in the MTC is 19.

- PDF files were for supplied for all but six of the 24 reports listed in the MTC bibliography (MS Appendix 8.4).

The MTC is divided into a number of networks, classified according to HBeAg status (positive / negative); and stratified by outcome measure and year. (NB. An MTC was not considered possible for the lamivudine-refractory patient group. A 'simple' indirect comparison was conducted – see section 3.1.5) The trials contributing data for each drug in each network are cited in MS Appendix 8.4.3, and the number of trials per drug are listed below (NB. Numbers of trials exceed 19 as some trials contribute data for more than one drug):

- Entecavir – data from six RCTs were included (of which five were included in the manufacturer's main assessment of clinical effectiveness, discussed above. These trials all compare entecavir with lamivudine, hence direct as well as indirect evidence was used), plus an additional unpublished phase III RCT comparing entecavir with adefovir in HBeAg positive nucleoside-naïve patients (BMS Trial A1463-079, unpublished).
- Lamivudine – data from a total of 16 RCTs were included (including data from the lamivudine comparator arms of the five entecavir RCTs included in the manufacturer's main assessment of clinical effectiveness).
- Telbivudine – data from three RCTs were included.
- Pegylated interferon alpha 2a – data from two RCTs were included.
- Adefovir in combination with lamivudine (in lamuvidine refractory patients) – data from three RCTs were included. (NB. As mentioned above, for this patient group a 'simple' indirect comparison was conducted).

The key characteristics of some, but not all, of the studies included in the MTC are tabulated in MS Appendix 8.4.6:

- 10 'non-entecavir' studies included in the MTC were tabulated in terms of key trial inclusion criteria, patient characteristics, outcomes, and efficacy results extracted for the MTC.
- The six entecavir studies are not tabulated. Five of these were already tabulated in greater detail in section 5.3 of the MS. It is not clear why the sixth study, BMS Trial A1463-079 which compares entecavir to adefovir, was not tabulated.
- The three remaining studies included in the MTC were not tabulated, and no explanation is given for this. However, it is presumed that the reason for their omission was because all of them were subsequently excluded from the MTC due to network redundancy (see MS Appendix 8.4.3).

No indication is given whether the methodology of the RCTs in the MTC was critically appraised. The ERG queried this with the manufacturer who clarified that no appraisal had been conducted (see Appendix 1).

The manufacturer makes no comment regarding how applicable the RCTs included in the MTC are to the scope of the appraisal and the decision problem. The trials, published between 1998 and 2007, were mostly drug company sponsored international phase II/III studies conducted in HBeAg positive patients. From examination of the table of study characteristics it appears that the trials predominantly featured Asian patients with compensated CHB, and excluded patients with co-infections and confounding medical conditions. Eligibility into the trials appears mainly to be on the basis of raised ALT and HBV DNA levels and histological evidence of necro-inflammation and fibrosis. Therefore, it can be taken that the trials included in the MTC appear generally to be applicable to the decision problem. However, the ERG has not systematically checked the study reports (where provided) in detail and it should be acknowledged that data are not reported consistently in the table, limiting the systematic assessment of applicability to the scope and decision problem.

There is also no discussion regarding how similar the trials are to each other. Given the time period over which they were conducted it would be reasonable to assume that there would be methodological differences as a consequence of technological innovations. For example, HBV DNA assays have evolved over recent years with lowering thresholds of viral response (detection). Some of the older trials use serum hybridization assays, whilst more recent trials use PCR and/or bDNA assays. In MS Appendix 8.4.3 it is stated that the outcome 'undetectable viral load', as reported by the various trials included in the MTC, corresponds to a threshold value of 300 copies/ML. However, it is unclear whether the assays used in some of the older trials are comparable with this threshold.

3.1.2.2 Details of any irrelevant studies that were included in the submission

The manufacturer presents a 'complete list' of RCTs comparing entecavir with other therapies' (MS Table 5.1) at the start of their clinical evidence section. The table provides brief details of the intervention / comparator, population, design, duration and objectives, but no results are

reported. No citation details are provided for these studies, other than the manufacturer's study reference number. It is not clear whether all of these trials have been completed and published. Of the 12 trials tabulated, only five actually met their inclusion criteria for systematic review. The remaining trials are excluded on factors such as insufficient duration (less than one year), and patient group (HIV/HBV co-infected patients). It is assumed that this table is presented to provide context around the more in-depth systematic review of entecavir which follows.

There do not appear to be any other irrelevant studies included in the submission.

3.1.2.3 Ongoing studies

MS section 5.2.5 provides details of on-going studies of entecavir from which additional evidence is anticipated within 12 months (NB. No publication dates given). Details of these studies are also reported in MS section 5.8 ('Non-RCT evidence').

- Study 901[19] is a long term observational study of open-label entecavir 1mg in nucleoside-naïve HBeAg positive and negative patients. The patients have entered the study following treatment in RCTs 022 (Chang *et al*)[12] and 027 (Lai *et al*)[17]. HBeAg positive patients from Study 022 will have been treated for five years, whilst HBeAg negative patients from Study 027 will have been treated over two to three years.
- The entecavir resistance cohort in which nucleoside-naïve and lamivudine-refractory patients will have been treated over a five year period. The cohort comprises patients from six entecavir clinical trials, and appears to be based, in part, on long-term data from study 901. A fuller description of long-term resistance monitoring is provided in section 3.3.1.6 of this report.
- An open-label extension study of Study 023 (Yao *et al*)[14] in HBeAg positive / negative Chinese patients, treated up to three years. (BMS Trial A1463-050).

3.1.2.4 Additional studies

The ERG did not identify any additional completed RCTs that are relevant for inclusion.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The MS provides a formal appraisal of the validity of the included trials using the quality assessment criteria developed by NICE (MS section 5.3.6). It is not stated whether the appraisal was conducted independently by more than one person.

- How was allocation concealed?

Allocation concealment was reported in the MS (p. 63) as double blind for all five RCTs but without any explanation of how the treatment allocation was concealed in each study. The CSRs (not the MS) mention that study, investigational and BMS personnel were blinded to the treatment allocation (treatment codes were held in a password-protected database that could not be accessed by study personnel, investigators or subjects). CSRs (not the MS) for all five RCTs state that a pharmacist at Bristol-Myers Squibb who was not involved in the study design, analysis or assessments was given access to treatment codes to permit efficient drug distribution. Procedures for blinding liver histology specimens are reported in appendices to the CSRs, but these appendices were not provided by the manufacturer. The CSR for RCT 014 (not the MS) mentions that blinding of drugs was achieved by both drugs being administered as capsules which had the same appearance. CSRs for the remaining four RCTs (not the MS) mention that entecavir was administered in tablets and lamivudine was administered in capsules, with blinding achieved by giving each patient both a tablet and a capsule (one active, the other placebo).

- What randomisation technique was used?

The method of randomization was reported briefly in the MS for all five RCTs and involved standard procedures for central allocation of treatment codes in all of the RCTs. The level of detail given about the randomization procedure in the MS differed between the RCTs. Randomization was stratified by site in all the RCTs and also stratified by patients' HBeAg status in one of the RCTs. Detailed randomization codes are given in appendices to the CSRs but were not provided in the MS. The MS does not comment on whether the reported randomization procedures have any particular strengths or weaknesses.

- Was follow-up adequate?

The question of whether follow-up was adequate was not directly addressed in the manufacturer's critical appraisal of studies (MS, p. 63). To answer this question would require some comment on the clinical relevance of the study timescales. The critical appraisal in the MS merely states for the RCTs that follow-up was at least 76 weeks and up to 96 or 120 weeks in

partial virological responders. The ERG noted that the majority of efficacy data provided in the MS are for 48 weeks. Given the chronic nature of HBV infection and long-term therapeutic requirements, the MS might more usefully have focused on the year two data, given that (i) the year one data duplicate those that are readily available in the published literature, and (ii) the MS does not expand on existing interpretations of those year one data that have already been published.

- Were the individuals undertaking the outcome assessment aware of allocation?

It is stated in the MS that individuals undertaking the outcomes assessments were unaware of the treatment allocation, but the MS provides no explanation of how this was achieved (perhaps reflecting the nature of Question 4 (MS, p. 63) which seems to require only a yes/no answer. As mentioned above, information reported in the CSRs indicates that outcome assessors would not have been aware of the treatment allocation in any of the RCTs until unblinding.

- Was a justification of the sample size provided?

The MS reports that the sample sizes were justified for tests of non-inferiority in Studies 022, 023 and 027 and for tests of superiority in Studies 014, 023 and 026 with statistical power of 90%. However, the MS does not mention whether the assessments of superiority in RCTs 014 and 026 would have required tests of non-inferiority as a prerequisite and, if so, whether the reported sample sizes would have provided adequate statistical power for these.

- Was the design parallel-group or crossover?

The MS reports accurately that all five of the RCTs included in the systematic review had parallel designs.

- Was the RCT conducted in the UK?

The geographical locations of the five RCTs are adequately summarized in the MS. Two RCTs (022, 027) were multinational and included some patients from the UK. Two other multinational RCTs (014, 026) included European but not UK patients. The remaining RCT (023) was conducted exclusively in China.

- How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?

The geographical composition of the RCTs is considered in the MS to be relevant to the cohort of patients likely to receive therapy for CHB in the UK. Both the HBeAg status of patients (positive or negative) and the provenance of the patients are relevant (both UK resident and immigrant patients receive CHB therapy in the UK). Most of the trials were multinational including European and Asian countries. The proportion of White patients in the trials varied from around 40% to 65%, and the proportion of Asian patients varied from 29% to 60% (One was exclusively in a Chinese population). The manufacturer's critical appraisal (MS, p. 64) does not comment on whether nucleoside-naïve and lamivudine-refractory patients would differ in their relevance to UK patient populations receiving CHB therapy. Although the patient population of Study 014 appears relevant to CHB therapy in the UK, the duration of dosing received by patients in this RCT was shorter (maximum 48 weeks) than in the other RCTs.

- Are the dosage regimens within those cited within the Summary of Product Characteristics?

The dosage regimens for both entecavir (0.5 mg/day or 1.0 mg/day) and lamivudine (100 mg/day) are correctly reported by the MS as being within those specified in the summaries of product characteristics.

- Were the study groups comparable?

The MS states that the study groups were comparable in each of the five RCTs but does not provide any further details. As only two of the RCTs provided p-values for baseline differences between the study groups, it is unclear to the ERG how the manufacturer deduced that the study groups were indeed comparable. The MS provides no comment on whether baseline characteristics differed between the RCTs. The ERG noted that prior interferon use was higher in Study 014 and 026 (40-55% of patients) than in Study 022, 023 and 027 (12-16% of patients) but the studies appear otherwise comparable in their baseline characteristics (other than the geographical differences mentioned previously).

- Were the statistical analyses used appropriate? Was an intention-to-treat (ITT) analysis undertaken?

The MS does not critically appraise the statistical analyses reported in the RCTs; it merely summarizes the key aspects of the analyses without adding further interpretation (MS, p. 65). It does not directly answer the question of whether the statistical analyses performed were

appropriate. An overall evaluation by the ERG of the statistical analyses reported in the MS is given below (section 3.1.5).

3.1.4 Description and critique of manufacturer's outcome selection

All of the outcome measures specified in the decision problem are presented in the manufacturer's assessment of clinical evidence, with the exception of time to treatment failure, survival (unless within the context of adverse events) and health related quality of life. These do not appear to have been outcome measures in any of the included clinical trials.

The primary outcome measure in Studies 022 and 027 was histological improvement, defined as improvement by at least two points in the Knodell necro-inflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline. In Study 023 a composite primary outcome was employed – the proportion of patients achieving an HBV DNA response (<0.7 MEq/ML) by bDNA assay and serum ALT <1.25 x ULN at week 48. Study 026 (Sherman *et al*; 2006[15]) employed two co-primary end-points, comprising histological improvement (as defined for Studies 022 and 027) and achievement of the composite end-point as in Study 023. In Study 014 the primary outcome was the proportion of patients who achieved undetectable HBV DNA (by bDNA assay) at week 24 (<0.7 MEq/ML).

Secondary outcome measures in the trials included reduction in HBV DNA levels from baseline to end-point; the proportion of patients achieving a viral load response or undetectable HBV DNA; decrease in the Ishak fibrosis score; HBeAg loss and seroconversion; normalisation of ALT, viral resistance; and adverse events.

Viral load (HBV DNA titre) was assessed using two quantitative analytical approaches. Branched-chain DNA (bDNA) assays have a threshold lower detection limit of around 0.7 mEq/mL. PCR-based assays, which have been developed more recently and are more sensitive, have a lower detection threshold of around 300-400 copies/mL. The ERG asked the manufacturer to clarify how comparable the thresholds are between the different assays. The manufacturer clarified that HBV DNA <0.7 mEq/mL is equivalent to 700,000 DNA copies/mL (See Appendix 1, page 3).

PCR-based assay results at 48 weeks were reported for all five RCTs (Table 6 in section 3.3.1.2), with results from bDNA assays also reported in two of the RCTs (see Table 7 in

section 3.3.1.2). Viral load as assessed by bDNA was a primary end-point in one RCT (014[10]) but was reported only at week 24 (Table 7).

The manufacturer did not provide any explanation as to the relative strengths and weaknesses of the two assay methods, nor how the thresholds for viral loads relate to disease state or treatment decisions. When viral load was included as a component of composite end-points (see section 3.3.1.5), the (less sensitive) estimate from bDNA assays was always used, without explanation. The ERG noted that in some of the manufacturer's clinical study reports (e.g. 023[20]) HBV DNA results by PCR assay are given both for <300 copies/mL and <400 copies/mL; however only the <300 copies/mL data are usually referred to in the manufacturer's submission.

3.1.5 Description and critique of the statistical approach used

The MS reports almost the same descriptions of the statistical methods used in the RCTs as reported in the published papers, but gives slightly more detail than the paper for Study 023. The published papers[12,17] and MS reported that for two RCTs (022, 027), a two-stage comparison of entecavir and lamivudine was carried out for the primary end-points. First, non-inferiority of entecavir compared to lamivudine was tested. If non-inferiority was demonstrated, a test of superiority of entecavir over lamivudine was then carried out. The MS (but not the published paper[14]) reports that this two-stage testing of non-inferiority and superiority was also applied in RCT 023. For the remaining RCTs (014, 026) the published papers[10,15] and MS state only that a test of superiority (entecavir over lamivudine) was carried out. Non-inferiority was inferred (Studies 022, 023, 027) if the lower limit of the two-sided 95% confidence interval for the difference in proportions of subjects achieving the specified end-point was greater than -10%. Superiority was defined for only two of the RCTs. For Study 014 the definition of superiority refers only to p-values and is unclear. For Study 026, superiority of entecavir was inferred if the 97.5% confidence interval for the estimate of the treatment differences was greater than zero. In this RCT, a Bonferroni adjustment was applied for testing superiority, but no reason is given in the paper or MS.

Overall, the statistical approaches reported in the published papers and MS relating to comparisons of entecavir against lamivudine in the RCTs appear generally appropriate. However, the statistical methods are reported superficially and have not been scrutinised in detail by the ERG. Differences in mean proportions of entecavir and lamivudine treated patients

were based on confidence intervals obtained from a normal approximation to the binomial distribution (mentioned for Studies 014, 023, 026 in the MS). Differences between means of continuous variables were tested using *t*-tests based on linear regression models that were adjusted for baseline characteristics or included baseline data as covariates (mentioned for Studies 014, 022, 023, 026 in the MS). The published papers and MS state that p-values reported in Studies 022 and 027 were not adjusted for multiple testing. Multiple testing is not mentioned for Studies 023 and 026, although in the latter RCT a Bonferroni correction was applied when assessing superiority (reason unclear; see above). The published paper for Study 014, in which three doses of entecavir and one dose of lamivudine were compared,[10] stated that the 2-sided significance level of α=0.05 was adjusted for three multiple comparisons (revised α=0.0167). The MS reports only one pairwise comparison from this RCT (one of the entecavir doses (1.0 mg/day) compared against lamivudine 100 mg/day), with no mention of multiple comparisons. The ERG assumes that α=0.05 (not 0.0167 as in the paper) would have been used for this comparison, although this is not mentioned in the MS.

According to the clinical study reports, data were analysed using two approaches. Non-completing patients were included in analyses as treatment failures (NC=F approach) and as missing data (NC=M approach). The data reported in the published papers are from the NC=F analyses. The MS does not clarify which analysis method was used; it refers sporadically to NC=F analysis for only some end-points in some RCTs (MS, p. 60, p. 81). Most of the year-one data given in the MS are the same as those reported in the published papers (i.e. based on NC=F analysis). However, data reported in the MS for the Ishak fibrosis score and HBeAg loss at week 48 in Study 026 (MS, page 79) are from the NC=M analysis. It is unclear whether this inconsistency reflects a typographic error (no explanation is given in the MS). The results obtained for these end-points in Study 026 are broadly similar for both NC=F and NC=M analysis approaches (sections 3.3.1.1 and 3.3.1.3).

P-values for baseline comparisons were given in only two of the published papers (Studies 022[12] & 027[17]) and exceeded 0.05 for all the reported variables. Published papers for the remaining trials (014, 023, 026) provided baseline variance (SD) estimates for selected variables and stated narratively that the treatment groups were well balanced at baseline for demographics and disease characteristics.[10,14,15] The baseline data reported in the MS forms a small and rather inconsistent subset of the baseline data available from the published papers. The MS does not report any of the baseline p-values given in the published papers for Studies

022 and 027. Baseline Ishak fibrosis scores are reported in the papers for Studies 022 & 027 but the MS reports these data for only Study 027. Prior interferon therapy data are reported in the published papers for Studies 014, 022, 023 and 027 but the MS reports these data only for Study 023. There are typographical errors in the MS in the reporting of viral genotype for Studies 026 and 027, but these are not relevant to the ERG assessment.

Estimates of variance (SD or SE) were not reported in the MS for any of the outcomes at the end of year one (48 weeks) that were evaluated by the ERG. An estimate of variance (SE) was given in the MS for only one of the outcomes (change from baseline in HBV DNA) in one of the RCTs (014). Confidence intervals were provided inconsistently both in the published papers and the MS for outcomes at 48 weeks. For Study 014, a confidence interval was reported in the MS only for the complete virological response, whilst for Study 023 no confidence intervals were provided for any of the outcomes. For the remaining studies (022, 026, 027), the MS provides confidence intervals for most of the outcomes.

Intent-to-treat (ITT) populations were reported inconsistently among the studies and publication types. All the RCTs mentioned an ITT population in their clinical study report, but only two (023, 026) mentioned it in their published paper.[14,15] The MS mentions ITT populations for three RCTs and defines ITT for two RCTs (Table 2). In most studies (014,[11] 022,[13] 026[16] & 027[18]) the analysis population was called 'modified ITT' (mentioned in the MS (p. 60-62) for studies 022 and 026) whilst for Study 023 it was referred to simply as 'ITT' (CSR[20] and MS, p. 61). The definition of the (modified) ITT population, where given, was all randomized patients who received ≥ 1 dose of study therapy.

Table 2 Reporting of intent-to-treat (ITT) populations in the RCTs and MS

	Study	014	022	023	026	027
Published paper	ITT mentioned	no	no	yes	yes	no
	ITT defined	no	no	no	yes	no
CSR	ITT mentioned	yes	yes	yes	yes	yes
	ITT defined	no	no	no	yes	yes
MS	ITT mentioned	no	yes (p. 60)	yes (p. 61, 65)	yes (p. 61)	no
	ITT defined	no	yes (p. 60)	no	yes (p. 61)	no

The MS presents results from the five RCTs separately, with little narrative summary and no meta-analysis undertaken of any of the five included trials for any of the outcomes to elucidate any overall effects of treatment. Aside from the inconsistencies noted above, in general the data presented in the year one data in the MS reflect the data reported in the published papers. The MS corrects some minor typographical errors which appeared in the primary publication for RCT 023 (see Table 6 and Table 12 in section 3.3.1 below).

The manufacturer does not give any reasons for not undertaking a meta-analysis, but proceeds directly to a network meta-analysis (MS section 5.5). The network meta-analysis notwithstanding, a pair-wise meta-analysis of entecavir versus lamivudine might have been a useful addition to the MS particularly since the MS does not provide much in the way of a narrative summary of the overall effect. It would also have provided information about any potential statistical heterogeneity between studies.

Mixed treatment comparison (MTC)

The manufacturer reports the methodology used to conduct a network meta-analysis (NMA – used synonymously under the heading of MTC) in section 5.5, with further detail in Appendix 8.4.

Separate networks were conducted for HBeAg negative and HBeAg positive, treatment-naïve patients, at year one and year two (year two predicted probabilities are cumulative rather than annual values). It was not considered possible to create a network for lamivudine-refractory patients (see below). The characteristics of the RCTs included in the MTC have been discussed earlier in section 3.1.2.1. The five RCTs comparing entecavir with lamivudine presented in the manufacturer's systematic review (MS section 5.2.3) are included in the MTC, hence both direct and indirect evidence is used.

The model was constructed using a Bayesian hierarchical approach using WinBUGs 1.4 software (the WinBUGs code is presented in MS Appendix 8.4.1 NB. The ERG has not examined this code). A burn-in period of 10,000 simulations was used to allow convergence, followed by 10,000 simulations for estimation. Entecavir is the baseline treatment common to all analyses, and absolute probabilities were estimated using the average rate observed across the entecavir arms at baseline. A fixed treatment effect model is used. However, no discussion or

rationale is presented for use of a fixed over a random effects model except that 'this form of analysis is discussed in more detail by a number of authors' (MS Appendix 8.4, page 2), citing journal articles on the methodology of MTC models.

The primary results are presented in terms of predicted probability that each drug attains a relevant end-point. The end-points analysed were:

- Proportion of patients with undetectable viral load below the limit of quantification (LOQ) by PCR.
- Proportion of patients achieving HBeAg seroconversion (applicable to the HBeAg positive networks only)
- Proportion of patients with histological improvement
- Proportion of patients with ALT normalisation

Log odds ratios and relative risks were also presented but only in the Appendix (MS Appendix 8.4). The results of the MTC are used in the economic model to estimate the cost-effectiveness of entecavir. (see section 4.4.1.2). A summary of the results of the MTC is reported in section 3.3.1.9 of this report.

The ERG consider the strengths of the MTC are:

- That it is supported by a reasonably sound systematic review process, in terms of the search strategy (see section 3.1.1.1), reporting of inclusion/exclusion criteria (see section 3.1.2.1) and tabulation of included evidence (see section 3.1.2.1). However, note the caveats discussed earlier in section 3.1.2.1, namely, ambiguity about the number of trials that were included; absence of any quality assessment of the trials; and inconsistent tabulation of the characteristics of included studies, limiting the assessment of the applicability of the included trials to the decision problem.
- The manufacturer has reported the outcome data extracted from the clinical trials that has been entered into the MTC, for each separate network at each year for each outcome (MS Appendix 8.4.3). This permits independent verification of the data used, although the ERG has not undertaken a systematic cross-checking with the trial publications. A visual representation of the networks and the trials populating them is provided in MS Appendix 8.4.4.

The ERG consider the weaknesses of the MTC are:

- That there are relatively few studies in some of the networks. For example, only two pegylated interferon alpha 2a RCTs are included, one in HBeAg positive and one HBeAg negative patients. Consequently the HBeAg positive and HBeAg negative networks contain only one RCT each. Furthermore, in the telbivudine HBeAg negative network only one RCT has been included. The manufacturer has used outcome data for the HBeAg negative sub-group from the GLOBE trial, a trial which had a mixed population of positive and negative patients. No discussion is given for the potential shortcomings of sub-group selection.
- There is a paucity of outcome data for year two treatment. The entecavir year two data are unpublished and will not have been subjected to the external journal peer review that the data from the other trials included in the MTC will have undergone. Pegylated interferon alpha 2a is omitted entirely from the network as no year two data were identified. Histological response to all interventions at year two was also omitted from the analysis due to lack of data.
- There is no definition of the criteria by which entecavir is judged to be 'significantly better' or 'equivalent' to other drugs.
- There is no assessment, or at the very least discussion, of heterogeneity (statistical or otherwise). The ERG asked the manufacturer to clarify whether heterogeneity had been assessed. The manufacturer clarified that there were insufficient data to allow a reliable estimate of a random effects variance to be obtained. (see Appendix 1).
- There is very little digest, discussion or reflection on the results of the MTC, and the methodology used to construct it in general.
- There is no discussion on how the results of the MTC compare to the results of the manufacturer's systematic review of entecavir (i.e. how mixed direct + indirect evidence compares with direct evidence).

Due to the issues raised above the ERG considers that results of the MTC are uncertain and should be interpreted with caution.

As mentioned earlier the MTC was only possible for nucleoside-naïve patients as it was suggested that there were insufficient data to build a network of studies in lamivudine resistant patients (see MS page 84-85). The manufacturer reports that there are relatively few clinical trials conducted in this population, and this seems a reasonable assertion. A 'simple' indirect comparison was provided for these patients on MS page 85 (table 5.6.5). Three trials, all

conducted in HBeAg positive patients, are included: Study 026 (Sherman *et al* 2006[11,15]); Perrillo *et al.* (2004)[5] and Peters *et al.* (2006)[6]. Using lamivudine as a common comparator, entecavir was compared with adefovir added to lamivudine. The studies are presented side by side in a table to permit visual examination of differences between entecavir and adefovir + lamivudine. The manufacturer asserts both that entecavir and adefovir added to lamivudine are statistically superior to lamivudine alone. Beyond this observation there is very little that can be reliably concluded about the relative efficacy of the two interventions. A pair-wise statistical indirect comparison using lamivudine as a common comparator and adjusted to take into account randomisation (along the lines of that suggested by Glenny *et al* (2005)[21]), may have been possible. However, no mention of such an approach is made.

The manufacturer also presents a 'descriptive' analysis of genotypic resistance rates for the drugs in section 5.6.6 (excluding pegylated interferon alpha 2a, which is not associated with resistance). It is acknowledged that an MTC was not possible as much of the data are from long-term observational studies. The manufacturer has therefore tabulated cumulative rates of resistance up to five years of follow-up, from a variety of sources. A caveat is provided that there are differences in populations and methodologies between these evidence sources. Caution is therefore required in the interpretation of this table.

3.2 Summary statement of manufacturer's approach

- The manufacturer has reported a systematic review of RCTs of entecavir, and a mixed treatment comparison model (MTC).
- The decision problem was similar to the scope of the appraisal, with some minor discrepancies. The decision problem does not include the use of entecavir in combination with other agents. However, it is not thought that any trials of entecavir as combination therapy have been conducted.
- The clinical effectiveness searches conducted by the manufacturer appear to be sound, although there were some limitations in how they have been reported. All of the databases recommended by NICE have been searched, plus additional databases. The search was designed to inform both the systematic review of entecavir RCTs, plus the MTC of entecavir and comparator drugs. The same set of search results were screened using criteria relevant to each. Both sets of inclusion criteria reflect the decision problem. Although the ERG has

not replicated the manufacturer's searches it appears that all relevant studies are likely to have been included.

- Five RCTs were included in the manufacturer's systematic review of entecavir. All of these appear to fully meet the manufacturer's inclusion criteria. Full data extraction (albeit with some minor typographical errors – see Appendix 1) and critical appraisal has been undertaken on all of these. Journal publications are available for all five RCTs, but only present outcome data up to 48 weeks. Outcome data up to week 96 are only available from commercial in confidence clinical study reports. The RCTs appear to be of generally good methodological quality, and are relevant to the decision problem.
- It appears that 19 studies were included in the MTC (NB. the manufacturer reported that there were 21 studies). Other than the five entecavir RCTs, these trials have not been subjected to critical appraisal, and there is limited data extraction. The ERG has not fully assessed whether these trials meet the inclusion criteria for the MTC or appraised their methodological quality. The key limitations of the MTC included lack of assessment and discussion of potential heterogeneity; no definition of statistical significance values or tests; and small number of studies / single studies in some networks. The results of the MTC are uncertain and should be interpreted with caution.
- The search strategy used to identify cost-effectiveness studies appears generally sound. Most of the databases recommended by NICE have been searched, and additional databases and websites are listed.

Quality assessment

The ERG has assessed the MS for its quality as a systematic review using the questions in CRD report 4. (Table 3).

3.3 Summary of submitted evidence

The following sub-sections summarise the results of the manufacturer's systematic review of entecavir. Each outcome measure is presented in turn, followed by a summary of results from the MTC.

Table 3 Quality assessment (CRD criteria) of the MS review of entecavir studies

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes – inclusion criteria presented for systematic review of entecavir; MTC model; and systematic review of licensed therapies for CHB. The inter-relationship between these three sets of inclusion criteria could have been reported in a more unified and explicit way. The criteria themselves accord with the decision problem.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes – searches appear generally sound.
3. Is the validity of included studies adequately assessed?	Yes – follows suggested NICE checklist
4. Is sufficient detail of the individual studies presented?	Partially • Systematic review of entecavir RCTs – characteristics and results of all five trials reported in detail. • MTC – limited details of study characteristics provided.
5. Are the primary studies summarised appropriately?	Uncertain • Systematic review of entecavir RCTs – very little synthesis of all five RCTs as a whole. The feasibility of a pair-wise meta-analysis is not discussed. • MTC – there are some limitations in the conduct and reporting of the MTC which prompts caution in the interpretation of its results.

3.3.1 Summary of results: manufacturer's systematic review

The results of the five RCTs included in the manufacturer's systematic review are summarised in the following sub-sections. The RCTs are referred to by their clinical study report code numbers (014, 022, 023, 026, 027). The data provided by the manufacturer for the first 48 weeks of each of these RCTs have all been published.[10,12,14,15,17] Data for a second year follow-up of each RCT were also provided, but have not been published. In one RCT (027) the year-2 data provided by the manufacturer are from the entecavir Summary of Product Characteristics.[8] In the remaining RCTs the year-2 data are from unpublished clinical study reports (014,[11] 022,[13] 023,[20] 026[16]). The majority of the data from the clinical study reports are marked as commercial in confidence (as indicated below).

3.3.1.1 Histological response

Three of the RCTs reported histological improvement at 48 weeks relative to baseline, defined as an decrease in the Knodell inflammatory score ≥ 2 points without concomitant increase (>1 point) in the Knodell fibrosis score (Table 4). In these RCTs, histological improvement was the primary (022[12], 027[17]) or a co-primary end-point (026[15]). In studies 022 and 027 the criterion for non-inferiority was met with respect to this outcome. The analyses then proceeded to testing for superiority. A significantly greater proportion of entecavir-treated than lamivudine-treated patients exhibited histological improvement in all cases, with a larger improvement in patients who received the higher entecavir dose (1.0mg/day). The same RCTs also reported improvement in the Ishak fibrosis score, defined as a decrease of ≥ 1 point at week 48 relative to baseline (

Table 5). A significant difference in the proportion of patients with improved Ishak score occurred only at the higher entecavir dose (1.0 mg/day), favouring entecavir treatment over lamivudine (RCT 026). The ERG noted that the data provided in the manufacturer's submission for this RCT (which are from an analysis in which non-completers were analysed as missing data; NC=M) differ from those given in the published paper[15] (which are from an analysis in which non-completers were analysed as treatment failures; NC=F) (section 3.1.5). However, these different analytical approaches yielded broadly similar results. No data beyond 48 weeks were given for histological improvement or Ishak fibrosis scores. Aside from the discrepancy noted above by the ERG, the histological data in the manufacturer's submission agree overall with those provided in the published papers.

Table 4 Proportion (%) of patients exhibiting histological improvement by week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	226 / 314 (72)	195 / 314 (62)	9.9 (2.6 to 17.2)	**0.009**
	027[17]	208 / 296 (70)	174 /287 (61)	9.6 (2.0 to 17.3)	**0.01**
1.0 mg/day	026[15]	68 / 124 (55)	32 / 116 (28)	27.3 (13.6 to 40.9)	**<0.0001**

Table 5 Proportion (%) of patients exhibiting improvement in the Ishak fibrosis score by week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	121 / 314 (39)	111 / 314 (35)	3.2 (-4.4 to 10.7)	0.41
	027[17]	107 / 296 (36)	109 / 287 (38)	[redacted]	0.65
1.0 mg/day	026[15]	[redacted] 42 / 124 (34) [c]	[redacted] 19 / 116 (16) [c]	[redacted] (6.8 to 28.2) [c]	[redacted] **0.0019** [c]

[a] Not given in the MS or published paper; extracted from the CSR[18] by the ERG.
[b] As reported in the MS; data conform to the NC=M analysis approach (non-completers analysed as missing data).
[c] As reported in the published paper[15] (data extracted by the ERG); data conform to the NC=F analysis approach (non-completers analysed as treatment failures).

3.3.1.2 Viral response

PCR-based assay results at 48 weeks were reported for all five RCTs (Table 6), with results from bDNA assays also reported in two of the RCTs (Table 7). Viral load as assessed by bDNA was a primary end-point in one RCT (014[10]) but was reported only at week 24 in the first year (Table 7). The ERG noted that in some of the manufacturer's clinical study reports (e.g. 023[20]) HBV DNA results by PCR assay are given both for <300 copies/mL and <400 copies/mL; however only the <300 copies/mL data are usually referred to in the manufacturer's submission.

Table 6 Proportion (%) of patients with undetectable HBV DNA at week 48, assayed by PCR method

Entecavir dose	Study [a]		Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		236 / 354 (67)	129 / 355 (36)	30.3 (23.3 to 37.3)	**<0.001**
	023[14]	HBeAg+	166 / 225 (74) [b]	83 / 221 (38)	-	-
		HBeAg-	31 / 33 (94)	29 / 40 (73)	-	-
		Total	197 / 258 (76)	112 / 261 (43)	-	**<0.001**

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	027[17]	293 / 325 (90)	225 / 313 (72)	18.3 (12.3 to 24.2)	**<0.001**
1.0 mg/day	014[10] [c]	11 / 42 (26) [c]	2 / 45 (4) [c]	[redacted]	**<0.01** [c,e]
	026[15]	27 / 141 (19)	2 / 145 (1)	(11.0 to 24.5)	**<0.0001**

[a] Threshold (lower limit of quantification) <300 copies/ml of HBV DNA unless stated otherwise.
[b] Incorrectly reported as 116 / 225 (74) in the published paper[14]
[c] Threshold <400 copies/ml of HBV DNA.
[d] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.
[e] Reported specifically in the CSR[11] as [redacted].

In all cases where viral load was reported at week 48, the proportion of patients with an undetectable viral load assayed by PCR (<300 or <400 copies/mL) (Table 6) or by bDNA (<0.7 mEq/mL) (Table 7) was significantly higher under 0.5 mg/day and 1.0 mg/day entecavir than 1.0 mg/day lamivudine treatment.

Table 7 Proportion (%) of patients with undetectable HBV DNA at week 48 assayed by bDNA method

Entecavir dose	Study [a]	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	322 / 354 (91)	232 / 355 (65)	25.6 (19.8 to 31.4)	**<0.001**
	027[17]	309 / 325 (95)	279 / 313 (89)	5.9 (1.8 to 10.1)	**0.005**
1.0 mg/day	014[10] [b]	33 /42 (79) [b]	6 / 45 (13) [b]	[redacted]	**<0.0001** [b]

[a] Threshold (lower limit of quantification) <0.7 mEq/ml (700,000 copies/mL) of HBV DNA.
[b] Reported for week 24 only
[c] Not reported in the MS or published paper; extracted from the CSR[11] by the ERG.

Virological response data for year two (not shown here) were reported for four of the RCTs (022[13], 023[20], 026[16], 027[8]). Data for year two are considered confidential by the manufacturer for studies 022 (p-value only), 023 and 026 (all data). The data for year two were reported for two patient cohorts but these cohorts are not clearly and consistently defined in the MS. The ERG consulted the individual clinical study reports for clarification and presumes that the year two cohorts reported in the submission are defined as follows:

- Partial virological responders / virological-only responders: patients who exhibited a virological response but (depending on the HBeAg status of patients in the study; section 3.1.2.1) did not exhibit serological or biochemical responses;
- The cumulative proportion of patients who had ever achieved a confirmed virological response through two years of treatment in two sequential measurements, or on the last on-treatment measurement.

[redacted]

3.3.1.3 HBeAg loss/seroconversion

The proportions of patients who exhibited seroconversion (appearance of HBeAg antibody and loss of HBe antigen) by 48 weeks were reported for four of the RCTs. Seroconversion occurred in similar proportions of entecavir and lamivudine treated patients, with none of the differences statistically significant (marginal statistical significance was almost reached in one RCT with lamivudine-refractory patients,[15] in which a larger proportion of patients who received 1.0 mg/day entecavir achieved seroconversion than those who received 1.0 mg/day lamivudine) (Table 8). HBeAg loss showed a similar pattern to seroconversion, with a difference between the drugs only evident in one study with lamivudine-refractory patients. In this RCT (026), the proportion of patients achieving seroconversion by 48 weeks was significantly greater with 1.0 mg/day entecavir than 1.0 mg/day lamivudine.[15] The ERG noted that the data provided in the manufacturer's submission for this RCT (which are from an analysis in which non-completers were analysed as missing data; NC=M) differ from those given in the published paper[15] (which are from an analysis in which non-completers were analysed as treatment failures; NC=F) (section 3.1.5). However, these different analytical approaches yielded similar results (Table 9).

Table 8 Proportion (%) of patients with seroconversion at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	74 / 354 (21)	64 / 355 (18)	2.9 (-2.9 to 8.7)	0.33
	023[14]	33 / 225 (15)	39 / 221 (18)	[redacted]	Stated NS [b]
1.0	014[10]	1 / 27 (4)	2 / 32 (6)	[redacted]	Stated NS [c]

mg/day	026[15]	11 / 141 (8)	4 / 145 (3)	5.0 (-0.1 to 10.2)	0.06

NS: not statistically significant (p>0.05)
[a] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.
[b] Reported specifically in the CSR[20] as [redacted].
[c] Reported specifically in the CSR[11] as [redacted].

Table 9 Proportion (%) of patients with HBeAg loss at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	78 / 354 (22)	70 / 355 (20)	2.3 (-3.7 to 8.3)	0.45
	023[14]	41 / 225 (18)	44 / 221 (20)	[redacted]	Stated NS [e]
1.0 mg/day	014[10]	3 / 27 (11)	3 / 32 (9)	[redacted]	Stated NS [f]
	026[15]	14 / 134 (10) [a] 14 / 141 (10) [b]	5 / 135 (4*) [a] 5 / 145 (3) [b]	[redacted]	[redacted]

[a] Data in the MS conform to the NC=M analysis approach (non-completers analysed as missing data).
[b] Data in the published paper[15] (not given in the MS; extracted by the ERG) conform to the NC=F analysis approach (non-completers analysed as treatment failures).
[c] Not reported in the MS or published paper; extracted from the CSRs by the ERG.
[d] The MS reports an incorrect confidence interval and p-value (given for the NC=F analysis instead of the NC=M analysis). The correct confidence interval and p-value have been extracted from the CSR[16] by the ERG.
[e] Reported specifically in the CSR[20] as [redacted].
[f] Reported specifically in the CSR[11] as [redacted].
* Rounded percentage reported as 3 in the MS.
NS: not statistically significant (p>0.05).

HBsAg loss by 48 weeks (an indicator of disease remission and an ultimate clinical goal), was reported for two RCTs. HBsAg loss occurred in fewer than 5% of HBeAg-positive patients overall, with no significant differences between the drugs (Table 10).

Table 10 Proportion (%) of patients with HBsAg loss at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	6 / 354 (2)	4 / 355 (1)	0.6 (-1.2 to 2.3)	0.52
	027[17]	1 / 325 (<1)	1 / 313 (<1)	[redacted]	[redacted]

[a] Not reported in the MS or published paper; extracted from the CSR[18] by the ERG.

Year two data for seroconversion and HBeAg loss (not shown here) were reported for three of the RCTs (022[13], 023[20], 026[16]), and for the two patient cohorts as defined above (3.3.1.2): (i) Partial virological responders (virologic-only responders). (ii) The cumulative proportion of patients who had ever achieved seroconversion through two years of treatment in two

sequential measurements, or on the last on-treatment measurement. For each of the end-points, statistical information (p-values) were only reported for the latter patient cohort. Note that the patient cohorts were not defined clearly in the MS; the ERG consulted clinical study reports for clarification (as in section 3.3.1.2). The year two results for seroconversion and HBeAg loss are considered confidential by the manufacturer for three of the four RCTs.

[redacted]

3.3.1.4 Biochemical response

The proportion of patients with a biochemical response, defined as alanine aminotransferase (ALT) titre at or below threshold (1.0 × upper limit of normal) at 48 weeks was reported in all five RCTs. For all of the patient groups and for both doses of entecavir, a significantly greater proportion of entecavir than lamivudine-treated patients achieved the biochemical response, with the largest difference at the higher entecavir dose (1.0 mg/day) (Table 11). These data in the manufacturer's submission are in agreement with the data presented in the published papers.

Table 11 Proportion (%) of patients with a biochemical response at week 48

Entecavir dose	Study		Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		242 / 354 (68)	213 / 355 (60)	8.4 (1.3 to 15.4)	**0.02**
	023[14]	HBeAg+	200 / 225 (89)	172 / 221 (78)	-	-
		HBeAg-	31 / 33 (94)	31 / 40 (78)	-	-
		Total	231 / 258 (90)	203 / 261 (78)	[redacted]	**0.0003**
	027[17]		253 / 325 (78)	222 / 313 (71)	6.9 (0.2 to 13.7)	**0.045**

1.0 mg/day	014[10] [a]	19 / 28 (68)	2 / 33 (6)	[redacted]	**<0.0001**
	026[15]	86 /141 (61)	22 / 145 (15)	51.7 (35.9 to 55.8)	**<0.0001**

[a] In Study 014 the results are for < 1.25 × upper limit of normal; results at week 48 are compared to the number of patients with abnormal baseline ALT.
[b] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.

The proportion of patients with a biochemical response at year two (not shown here) was reported in four of the RCTs (022[13], 023[20], 026[16], 027[8]). The data are considered confidential by the manufacturer in studies 022 (p-value only), 026 (most data) and 023 (all data).

[redacted]

3.3.1.5 Composite ('protocol-defined' or 'complete response') end-points

Composite end-points, also referred to as 'protocol defined' or 'complete response' end-points, comprised combinations of viral response, biochemical response and/or HBeAg loss. Composite end-points were used in all five RCTs to assess patients' disease status and improvement at the end of the first year and to determine their treatment course in year two. A composite end-point was specified as the primary end-point in Study 023 and as a co-primary end-point in Study 026. The viral response component of the composite end-points was always determined by bDNA assay (not PCR-based assay), with threshold HBV DNA <700,000 copies/mL (0.7 mEq). The biochemical response component was defined as ALT titre < 1.25 × the upper limit of normal. Three composite end-points were reported in the primary studies; these differed according to which of the three components (viral, biochemical, and HBeAg loss) they included (Table 12).

The proportion of patients who achieved a complete response by week 48 as indicated by the composite end-point was usually higher for entecavir-treated than lamivudine-treated patients

(most RCTs), or did not differ between the drugs (Study 022, and HBeAg-positive patients in Study 014); in no cases was lamivudine favoured. The largest differences occurred in comparisons involving patients who received the higher entecavir dose (1.0 mg/day). Where p-values were reported, the differences between drugs were statistically significant, except among the HBeAg-positive and HBeAg-negative patient sub-groups in Study 014, which had relatively small sample sizes (Table 12).

The proportions of patients who achieved a complete (composite) response in year two (not shown here) were reported for two RCTs (022[13], 026[16]) for partial virological responders (virologic-only responders). These data (both RCTs) are considered confidential by the manufacturer.

[redacted]

Table 12 Proportion (%) of patients achieving a composite end-point at week 48

Entecavir dose	Study		End-point [a]	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		1[b]	74 / 354 (21)	67 / 355 (19)	[redacted]	[redacted]
	023[14]	HBeAg+	2	199 / 225 (88) [c]	143 / 221 (65)	-	-
		HBeAg-	2	32 / 33 (97)	31 / 40 (78)	-	-
		Total	2	231 / 258 (90)	174 / 261 (67)	[redacted]	**<0.0001**
	027[17]		2	275 / 325 (85)	245 / 313 (78)	6.4 (0.3 to 12.4)	**0.04**
1.0 mg/day	014[10]	HBeAg+	3	2 / 27 (7)	2 / 32 (6)	-	Stated NS
		HBeAg-	3	10 / 15 (67)	0 / 13 (0)	-	Stated NS
		Total	3	12 / 42 (29)	2/ 45 (4)	24.1 (8.7 to 39.6)	**<0.01** [f]
	026[15]		2	77 / 141 (55)	6 / 145 (4)	50.5 (40.4 to 60.6)	**<0.0001**
			3	13 / 141 (9)	1 / 145 (<1)	8.5 (3.6 to 13.5)	**0.0008**

[a] Definition of composite end-point:
1. HBV DNA (bDNA assay) < 0.7 MEq/mL and HBeAg loss
2. HBV DNA (bDNA assay) < 0.7 MEq/mL and ALT < 1.25× upper limit of normal
3. HBV DNA (bDNA assay) < 0.7 MEq/mL and ALT < 1.25× upper limit of normal and HBeAg loss

[b] Incorrectly reported on p. 65 of the MS; the manufacturer confirmed that the end-point definition on p. 65 of the MS is a typographical error (A9 in Appendix 1).

[c] Incorrectly reported as 119 / 225 (88) in the published paper.[14]
[d] Not given in the MS or published paper, but provided by the manufacturer (from CSR[13]) in response to a query (A10 in Appendix 1).
[e] Not given in the MS or published paper; extracted from the CSR[20] by the ERG.
[f] Reported specifically as [redacted] in the CSR.[11]
NS: not statistically significant (p>0.05).

3.3.1.6 Viral resistance

The manufacturer's submission presents entecavir resistance monitoring data up to four years. These data were obtained from patients who had been initially treated with entecavir in RCT 022,[12,13] and had then entered a four-year open-label extension study of antiviral activity and safety (Study 901). Data were also obtained from the entecavir four-year resistance monitoring programme.[22] This monitoring programme included patients from RCT 022 who had continued into Study 901, together with patients from RCTs 014, 026 and 027, and an additional RCT (015), who had also continued into Study 901. The disposition of patients in terms of how many had continued from each of these RCTs into the extension Study 901 is difficult to follow. The ERG were unable to check and appraise this in detail because the manufacturer did not submit a clinical study report for Study 901 (only a poster abstract[23] was provided). The manufacturer also did not provide any of the appendices cited in the entecavir resistance monitoring programme report[22] that describe patient flow.

Strictly, patients who entered Study 901 could be considered outside the scope of the current assessment, as they were initially administered a combination of entecavir and lamivudine before returning to entecavir monotherapy (all patients received 1.0 mg/day entecavir). The combination therapy differed depending on the provenance of patients on entry into Study 901.

- Patients from RCT 022 initially received 1.0 mg/day entecavir + 100 mg/day lamivudine then proceeded to1.0 mg/day entecavir monotherapy.
- Patients from other RCTs initially received 0.5 mg/day entecavir + 100 mg/day lamivudine, changed to 1.0 mg/day entecavir + 1.0 mg/day lamivudine, then proceeded to 1.0 mg/day entecavir monotherapy.

The median duration of the combination therapy in Study 901 was reported in the MS as 13 weeks, but without any indication of the range or variance, or whether it differed among patient groups or provenance. The duration of the subsequent entecavir monotherapy in Study 901 was only reported vaguely in the manufacturer's submission as 'long term'. The ERG noted that

some of the entecavir resistance data from Study 901 included patients (from RCT 015) who had received liver transplants. These patients are outside the scope of the current appraisal, but are not separated in a conference abstract[24] and report abstract[22] that summarize the results of Study 901, and are not mentioned in the manufacturer's submission.

As the MS concerning entecavir resistance appears to be based on information outside the scope of the current appraisal, the ERG considered resistance data in RCTs 014, 022, 023, 026 and 027 that clearly are within the scope. Unfortunately these data are limited, at most, to two years. Information available from the published papers and clinical study reports is summarized below for year one and, where available, year two of these RCTs. The ERG noted that none of the data summarised below were given in the MS report. (As the year two data come from the clinical study reports these are considered confidential.)

Resistance analysis in year one (48 weeks) was reported in four studies (014,[10] 022,[12] 026,[15] 027[17]). The procedure involved PCR amplification and sequencing to identify the nucleotide sequence of the HBV reverse transcriptase domain of the HBV polymerase gene. Emergent substitutions were identified by comparison with patients' nucleotide sequence at baseline. Resistance was deduced if patients with virologic rebound (defined as a confirmed increase in HBV DNA ≥ 1 $\log_{10}$ copy/mL from the nadir value according to PCR assay during treatment) had substitutions known to confer resistance. In two trials (022,[12] 027[17]), resistance was also verified using cell culture phenotypic assays with entecavir (in which the emergent substitutions were inserted into recombinant cell culture clones). Resistance genotyping for entecavir was reported for patients with relevant pairs of baseline and 48-week data and for those who experienced virologic rebound; resistance data for lamivudine was reported, less consistently, in three of the RCTs (Table 13).

Table 13 Patient groups analysed for anti-viral drug resistance up to week 48

Study	All available patients with paired baseline & week 48 data	Patients with virologic rebound
014[10]	entecavir, lamivudine [a]	entecavir (but n=0 for 1.0mg/day dose)
022[12]	entecavir	entecavir, lamivudine
026[15]	entecavir	entecavir
027[17]	entecavir [b]	entecavir, lamivudine

[a] Number of patients not specified [b] Used a random subset (211) of the available patients

The proportion of entecavir-treated patients who experienced virologic rebound by week 48 was low (≤2%) in all cases. A larger proportion of lamivudine-treated patients experienced virologic rebound (8% & 18%; reported in two RCTs only) (Table 14). Most of the entecavir-treated patients analysed by week 48 did not have any detectable resistance-associated substitutions. The entecavir patients with resistance-associated substitutions (7/134 overall and 2/2 virological rebound patients in one RCT) were receiving the higher entecavir dose (1.0 mg/day) (Table 15). The majority of lamivudine-treated patients who experienced virological rebound and for whom data are available (two RCTs only) had detectable resistance-associated substitutions by week 48 (Table 15).

Table 14 Number (%) of patients with virologic rebound up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day
0.5 mg/day	022[12]	6 (2)	63 (18)
	027[17]	5 (2)	25 (8)
1.0 mg/day	014[10]	0 (0)	-
	026[15]	2 (1.4)	-

Table 15 Proportion of patients with antiviral-resistant substitutions by week 48

Entecavir dose	Study [a]	Entecavir			Lamivudine 100mg/day		
		0 weeks	48 weeks [b]	Virologic rebound patients	0 weeks	48 weeks [b]	Virologic rebound patients
0.5 mg/day	022[12]	-	0 / 339 (E)	0 / 6 (E) [e]	-	-	45 / 63 (L)
	027[17]	-	0 / 211 (E)	0 / 5 (E) [e]	-	-	20 / 25 (L)
1.0 mg/day	014[10]	38 / 42 (L)	0 / 42 (E) [c]	-	39 / 45 (L)	-	-
	026[15]	118 / 141 (L)	7 / 134 (E) [d]	2 / 2 (E)	124 / 145 (L)	-	-

[a] (E): entecavir-resistant substitutions; (L): lamivudine-resistant substitutions.
[b] For patients that had paired baseline and 48-week data.
[c] 2 resistant substitutions were observed in entecavir patients on other doses (0.1 & 0.5 mg/day).
[d] none of these 7 patients experienced virologic rebound.
[e] these patients retained full sensitivity to entecavir in phenotypic assays at week 48.

[redacted]

[redacted]

Data on drug resistance in year two was only given in a clinical study report for one RCT (027[18]), and only for lamivudine-treated patients who had experienced virologic rebound (no entecavir-treated patients had experienced virologic rebound in this study in year two).

[redacted] Clinical study reports for the other RCTs mention that further resistance data may be available in other unpublished reports. However, these reports were not submitted by the manufacturer and are not accessible to the ERG.

3.3.1.7 Adverse events

Adverse events up to 48 weeks were reported in all five of the RCTs included in the manufacturer's systematic review. The proportions of patients with any adverse events (Table 16), or serious adverse events (Table 17) were similar for entecavir (either dose) and lamivudine. The number of deaths during treatment was low (<1% in all cases) (Table 18). Statistical tests, which were reported only in two of the RCTs, indicated no significant differences between the drugs in the frequency or seriousness of adverse events, or the frequency of deaths (p>0.3 in all comparisons).

The proportion of patients who withdrew during the first year due to adverse events was similar for entecavir and lamivudine in three RCTs (023,[14] 027,[17] 014[10]). In the remaining RCTs (022,[12] 026[15]), more lamivudine-treated than entecavir-treated patients withdrew. The difference was statistically significant in one of these RCTs,[12] but no statistics were reported in the other (Table 19).

Table 16 Proportion (%) of patients with any adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	306 / 354 (86)	297 / 355 (84)	0.34
	023[14]	154 / 258 (60)	145 / 261 (56)	-

	027[17]	246 / 325 (76)	248 / 313 (79)	0.30
1.0 mg/day	014[10]	36 / 42 (86)	38 / 45 (84)	-
	026[15]	120 / 141 (85)	117 / 145 (81)	-

Table 17 Proportion (%) of patients with serious adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	27 / 354 (8)	30 / 355 (8)	0.78
	023[14]	9 / 258 (3)	12 / 261 (5)	-
	027[17]	21 / 325 (6)	24 / 313 (8)	0.64
1.0 mg/day	014[10]	5 / 42 (12)	3 / 45 (7)	-
	026[15]	14 / 141 (10)	11 / 145 (8)	-

Table 18 Proportion (%) of deaths up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	0 / 354 (0)	2 / 355 (<1)	0.50
	023[14]	0 / 258 (0)	0 / 261 (0)	-
	027[17]	2 / 325 (<1)	0 / 313 (0)	0.50
1.0 mg/day	014[10]	0 / 42 (0)	0 / 45 (0)	-
	026[15]	1 / 141 (<1)	2 / 145 (<1)	-

Table 19 Proportion (%) of patients discontinuing due to adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	1 / 354 (<1)	9 / 355 (3)	**0.02**
	023[14]	1 / 258 (<1)	3 / 261 (1)	-
	027[17]	6 / 325 (2)	9 / 313 (3)	0.44
1.0 mg/day	014[10]	3 / 42 (7)	4 / 45 (9)	-
	026[15]	2 / 141 (1)	10 / 145 (7)	-

In all five RCTs, more lamivudine-treated than entecavir-treated patients had experienced an alanine aminotransferase (ALT) flare by week 48. However, the differences were small in 023[14] (no statistics reported) and 027[17] (p>0.3) (Table 20). The differences were larger in the

remaining RCTs (014,[10] 022,[12] 026[15]), but statistics were only reported in one of these (022,[12]). In that trial, the difference in frequency of ALT flares between drugs was statistically significant if an ALT flare was defined as ALT titre > 2× baseline and > 5× upper limit of normal (p=0.02), but not significant if an ALT flare was defined as ALT titre > 2× baseline and > 10 × upper limit of normal (p=0.08) (Table 20).

In addition to safety data for the first year of entecavir treatment, which is from the published papers[10,12,14,15,17] (as reproduced above), the manufacturer's submission also directly reproduces the safety data given in the Summary of Product Characteristics for entecavir.[8] Some of these data represent safety monitoring up to 96 or 107 weeks. However, the ERG is unable to comment on the validity of these data or their relevance to the current assessment, as the Summary of Product Characteristics does not identify the sources of its data, it provides only a superficial summary of the studies and their patients' characteristics, and it does not clearly identify the timing of the reported observations.

Table 20 Proportion (%) of patients experiencing an ALT flare up to week 48

Entecavir dose	Study	ALT flare definition [a]	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	1	12 / 354 (3)	23 / 355 (6)	0.08
		2	37 / 354 (10)	59 / 355 (17)	**0.02**
	023[14]	1	11 / 258 (4)	15 / 261 (6)	-
	027[17]	1	3 / 325 (<1)	5 / 313 (2)	0.50
		2	6 / 325 (2)	10 / 313 (3)	0.32
1.0 mg/day	014[10]	3	7 / 42 (17)	15 / 45 (33)	-
	026[15]	1	1 / 141 (<1)	16 / 145 (11)	-

[a] ALT flare definitions:
1. ALT > 2× baseline and > 10× upper limit of normal
2. ALT > 2× baseline and > 5× upper limit of normal
3. ALT > 2× baseline

[redacted] The safety data reported in the manufacturer's submission up to 48 weeks and the cumulative safety data reported in the clinical study reports up to the end of each study in year two are in good agreement for the five safety end-points considered above. The

number of patients in each treatment who exhibited each of these end-points in year one (Table 16 to Table 20) differed by <5% from the total number who exhibited these end-points up to the end of dosing in year two.

3.3.1.8 Health Related Quality of life

None of the five randomized controlled trials reported health related quality of life as an outcome measure

3.3.1.9 Results of the mixed treatment comparison (MTC)

Results of the MTC in nucleoside-naïve patients are reported in section 5.6.4 of the MS. Results of the 'simple' indirect comparison in lamivudine resistant patients are reported in MS section 5.6.5. Given the extreme limitations of the latter analysis (as discussed earlier – see section 3.1.5) the results will not be presented here. Similarly, a 'descriptive comparison' of cumulative genotypic resistance rates for entecavir and comparator drugs is tabulated in MS section 5.6.6. However, results are not presented in the current report.

As mentioned in section 3.1.5, there are limitations in the conduct and reporting of the MTC and its findings should be interpreted with caution. Furthermore, due to paucity of data the predicted probability of histological response for all drugs was only estimated at year one. The probability of response on any outcome for pegylated interferon alpha 2a was also only estimated at year one.

The results of the MTC suggest that entecavir is either significantly better or equivalent to comparators, depending on the outcome measure and the time-point. It is not clear, however, on what basis either of these assertions have been defined.

In HBeAg positive, treatment-naïve patients:

- HBV DNA response - entecavir had a significantly higher predicted probability at years one and two compared to all comparators.
- HBeAg seroconversion - entecavir was reported to be equivalent to all comparators in the predicted probability at both years.

- ALT normalisation - entecavir had a significantly higher predicted probability than lamivudine (at both years) and pegylated interferon alpha 2a (year one), and was reported to be 'equivalent' to telbivudine (at both years).
- Histological improvement - entecavir had a significantly higher predicted probability of compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. pegylated interferon alpha 2a was omitted from this analysis).

Among HBeAg negative, treatment naïve patients:

- HBV DNA response - entecavir had a significantly higher predicted probability at years one and two compared with lamivudine and pegylated interferon alpha 2a, and was reported to be equivalent to telbivudine at both years.
- ALT normalisation - entecavir had a significantly higher predicted probability than all comparators at year one, but appeared similar to comparators at year two.
- Histological improvement - entecavir had a significantly higher predicted probability compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. Pegylated interferon alpha 2a was omitted from this analysis).

The manufacturer does not make any comparison of the results of the MTC with the results of the systematic review of entecavir RCTs. Specifically, whether the results of the mixed comparison of direct and indirect evidence for entecavir versus lamivudine accord with the direct evidence for the two drugs from pair-wise comparison in RCTs. The manufacturer's review of the RCTs, as summarised in the previous sub-sections, generally show entecavir to be statistically superior to lamivudine across outcomes. In the MTC entecavir was likewise reported to be statistically superior to lamivudine, with the exception of HBeAg seroconversion where it was classed as equivalent. The head to head RCTs reported a statistically insignificant difference between the drugs on this outcome, which cannot necessarily be interpreted as equivalence.

3.4 Summary

Overall the MS provides an unbiased estimate of treatment efficacy for entecavir based on the results of the systematic review of RCTs. All five of the included RCTs compared entecavir with lamivudine. The results show that there are statistically significant differences between the two drugs favouring entecavir on most outcomes at one year of treatment. No quantitative pair-wise

meta-analysis was undertaken of these five RCTs so there is no overall estimate of treatment effect.

In order to fully address the decision problem an MTC was conducted which provided an estimate of the treatment effect of entecavir in relation to lamivudine, telbivudine, and pegylated interferon alpha 2a in nucleoside-naïve patients (NB. An MTC was not presented for the lamivudine-refractory patient group). It cannot necessarily be concluded that the MTC provides an unbiased estimate of treatment efficacy due to shortcomings in the methodology and reporting of the model (as discussed in section 3.1.5).

The manufacturer has provided an interpretation of the evidence from the systematic review and the MTC in MS section 5.9. The key assertion is that entecavir is clinically effective in nucleoside-naïve patients, with an acceptable safety profile and low rates of resistance compared with lamivudine. Based on the published RCTs this assertion would seem founded.

The manufacturer makes a number of assertions about the comparative efficacy of entecavir with the other comparators in the decision problem, based on the MTC and from non-statistical indirect comparison of cumulative resistance rates. Namely:

- Entecavir is superior in the probability of achieving undetectable viral load, and is associated with lower genotypic resistance rates compared with telbivudine in nucleoside-naïve patients.
- Entecavir is superior to pegylated interferon alpha 2a in nucleoside-naïve patients in terms of viral suppression and ALT normalisation, and equivalent in terms of HBeAg seroconversion (HBeAg positive patients only, by definition), and has a lower rate of adverse events.

The ERG suggests that these assertions are not justified based on the results of the MTC.

The MS also notes that entecavir is a more clinically effective option compared with continuing lamivudine therapy it terms of viral suppression. This is based on head-to-head RCT evidence and the ERG considers this a reasonable interpretation of the evidence. The MS states that there is a lack of data to enable the decision problem to be answered in terms of the comparative efficacy of entecavir versus adefovir added to lamivudine in lamivudine-refractory

patients. This is a reasonable assertion and the ERG do not know of any additional evidence in this patient group that is not included in the submission.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

(i) a review of published economic evaluations of interferon alpha, pegylated interferon alpha 2a, lamivudine, adefovir and entecavir used as the first line treatment in nucleoside naïve CHB patients. The MS also reviewed economic evaluations of adefovir and entecavir as a salvage therapy in patients who became resistant to lamivudine. The search strategy to identify published literature is reported in section 6.1.1 of the MS and appraised in section 3.1.1.1. Searches were conducted between September 5th and October 10th, 2007. Appendix 8.6 of the MS presents summaries of nine studies included in the review. The ERG identified another relevant economic evaluation of entecavir vs lamivudine with adefovir as salvage therapy in HBeAg positive patients (Veenstra *et al*, 2007[25]), which was not included in the review.

(ii) a report of an economic evaluation undertaken for the NICE STA process. Entecavir as a first line treatment is compared with lamivudine, pegylated interferon alpha 2a, and telbivudine as monotherapy treatments. The cost-effectiveness of entecavir in nucleoside treatment naïve CHB patients is estimated separately for two mutually exclusive sub-groups: HBeAg positive patients and HBeAg negative patients. The base case results of the economic analysis are presented in the MS Tables 6.11-6.12 as a set of estimates of an incremental cost per QALY gained for entecavir in comparison to lamivudine, pegylated interferon alpha 2a, and telbivudine. In addition, the cost-effectiveness of entecavir vs a combination therapy of lamivudine with adefovir is estimated in HBeAg positive patients who have developed resistance to lamivudine. In this model it is implicitly assumed that entecavir is a second line (salvage) therapy in a sub-group of lamivudine-resistant patients and is compared to the alternative combination therapy of lamivudine with adefovir.

4.2 Cost effectiveness analysis (CEA) methods

The CEA consists of two Markov state transition models for HBeAg positive patients (HBeAg positive disease model) and HBeAg negative patients (HBeAg negative disease model) that

estimate the effect of treatment with entecavir and the comparators lamivudine, pegylated interferon alpha 2a, and telbivudine. Both models have a lifetime horizon and a cycle length of one year, with the half-cycle correction applied. In addition the HBeAg positive disease model is used to estimate the cost-effectiveness of entecavir vs a combination of lamivudine with adefovir in HBeAg positive patients who have developed resistance to lamivudine. The results from the economic evaluation using the HBeAg positive disease model are presented for the base case assumptions, with two years of treatment with entecavir and the comparators, except for pegylated interferon alpha 2a which is administered for one year.

The base case analysis in the HBeAg negative disease model assumes five-year treatment duration for all the therapies but pegylated interferon alpha 2a, which is administered for one year, after which the non-responding patients are switched to lamivudine for the remaining four years.

A cost-effectiveness analysis of the lifetime treatment duration is explored in the scenario analysis using the HBeAg negative disease model.

4.2.1 Natural history

The disease progression pathway adopted for the HBeAg positive disease model includes 14 mutually exclusive health states. Patients enter the model in the “chronic HBV” health state and receive entecavir or one of the comparator treatments. In accordance with the natural history of the disease, patients then may remain in this state, achieve treatment-induced response (HBeAg seroconversion), experience treatment relapse (return to CHB) or alternatively achieve HBsAg loss where the patients are effectively cured. Patients could also develop resistance to the active treatment (a virological breakthrough) with or without a severe hepatic flare (defined as ALT>10 x upper limit of normal). Patients who do not achieve HBeAg seroconversion can also enter more progressive stages of liver disease (such as active cirrhosis and decompensated cirrhosis). A specific feature of the model is an “inactive” cirrhosis health state that only HBeAg seroconverted patients could enter. This health state is associated with a significantly lower risk of decompensation than the active cirrhosis health state. All patients are assumed to be at HCC risk except for those who had experienced HBsAg loss or who received a liver transplant.

The 14 health states featured in the HBeAg positive disease model are also present in the HBeAg negative disease model. However, in the HBeAg negative sub-group of patients, treatment outcomes are defined in terms of viral suppression (e.g. undetectable viral load below the LLOQ by PCR assay). In addition, in the HBeAg negative disease model, patients may achieve response to the initial treatment, or, following a virological breakthrough, subsequently receive and respond to salvage treatment. This is reflected in two different response states (response to the initial treatment and response to salvage therapy), resulting in the total number of 15 health states in the HBeAg negative disease model.

In both models a response (either HBeAg seroconversion or an undetectable viral load in the HBeAg negative disease model) may occur spontaneously as well as being achieved in the course of treatment. All cause mortality, in addition to the mortality risk associated with CHB, was accounted for in both models.

Table 6.3 of the MS presents transition probabilities used in the natural history model for HBeAg positive and HBeAg negative sub-groups of CHB patients. Although the MS does not elaborate on the differences in the natural disease progression between the sub-groups, it can be deduced from Table 6.3 that the baseline risk of compensated cirrhosis is assumed to be higher in the HBeAg negative sub-group. This is consistent with available clinical evidence (EASL, 2003[26]) and the assumptions used in previous modelled economic evaluations of anti-CHB treatments (Shepherd *et al*, 2006)[7].

4.2.2 Treatment effectiveness

Tables 6.4 and 6.5 of the MS present treatment effects that replace the relevant natural history transition probabilities for HBeAg positive and HBeAg negative populations respectively. The estimates of response to treatment used for the base case are taken from the network meta-analyses described in section 5.6 of the MS and in Appendix 8.4.

The estimates of risks of developing resistance to active treatment came from published clinical trials (Lai *et al*, 2005 [27], Lau *et al*, 2005[28], Marcellin *et al*, 2004[29]), open-label extensions of RCT (Lee *et al*, 2006[30], Han *et al*, 2007[31]), unpublished entecavir clinical study reports (CSR[13,18,22] and observational studies (Lok *et al*, 2003[32], Di Marco *et al*, 2004[33]).

In addition, the HBeAg positive disease model and the lamivudine-refractory model use differential transition probabilities of developing compensated cirrhosis in patients who achieve viral load suppression, although they do not achieve HBeAg seroconversion. The risk is the lowest in patients treated with entecavir and the highest (almost equal to the baseline cirrhosis risk of 4.4%) in patients treated with pegylated interferon alpha 2a. The source of clinical evidence and the method of deriving relative risks for alternative treatments are presented in sections 6.2.7-6.2.8 of the MS.

The MS stated that due to the paucity of clinical effectiveness data in HBeAg positive lamivudine–refractory patients the network meta-analysis was not conducted. The estimates of clinical effectiveness of entecavir treatment (seroconversion rates, resistance rates and risk of developing compensated cirrhosis) in this sub-group were obtained from the journal publication for Study 026 (Sherman *et al*)[15], plus unpublished entecavir clinical study reports (CSR) [16 22] and an observational study (Buti *et al*, 2007)[34]. Estimates of seroconversion rates in patients treated with a combination of lamivudine and adefovir were obtained by averaging the response rates observed in two small RCTs (Peters *et al*, 2004[6], Perillo *et al*, 2004[5]).

4.2.3 Health related quality-of-life

The MS models assume that health states corresponding to the stages of natural disease progression (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) determine the patients' quality of life. This is consistent with approaches used in previously published economic evaluations (Wong *et al*, 1995 [35], Veestra *et al*, 2007[25], Shepherd *et al*, 2006 [7]). Utility values were obtained from a recent study by Levy *et al* (2007)[36]. In this study standard gamble utilities were elicited using an interviewer-administered survey from populations in six countries with a total of 534 CHB-infected patients and a total of 600 uninfected respondents. The sex-age adjusted utility values elicited from 100 uninfected respondents in the UK were used in the model. Details are discussed in section 4.4.1.2 of this report.

The adverse effects of pegylated interferon alpha 2a and the associated reduction in HRQoL were reflected in a utility decrement, which applied to the CHB state for the duration of therapy. This is consistent with the assumptions used in other published economic evaluations (Veenstra *et al*, 2007 [25], Wong *et al*, 1995 [35]).

4.2.4 Resources and costs

Two types of costs are used in the models: cost of medications (an initially prescribed drug and a salvage therapy whenever applicable) and the aggregated costs of monitoring and treating patients in different health states.

- Dose data were obtained from the summaries of product characteristics [37] [38] [39] [40] [41]. Unit costs for the standard doses were obtained from the most recent version of the British National Formulary[42]. The following assumptions in estimation of drug costs were used:
    - a full compliance of patients to treatment regimens;
    - the number of physician visits and investigative tests associated with active treatment was assumed to be identical across treatment groups, therefore the associated costs were not included in the model;
    - costs associated with treatment of adverse effects were also assumed to be identical across treatment groups and excluded from the model;
- Estimates of the costs of management of patients in different health states (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) were taken from Shepherd *et al* (2006)[7] and adjusted to 2007 price equivalents using the Gross Domestic Product (GDP) deflator. The reason for choosing the GDP deflator over the Health Service Cost Index (HSCI) is not explained in the MS. Health state costs adopted for economic evaluation reported in Shepherd *et al* (2006)[7] were "a combination of values estimated specifically for this assessment, based on treatment protocols developed with expert advisors to the project and costed with the assistance of the finance department at Southampton University Hospitals Trust, and published cost estimates for the progressive stages of liver disease".

4.2.5 Discounting

A discount rate of 3.5% was applied to both costs and outcomes at each cycle of HBeAg positive and HBeAg negative disease models.

4.2.6 Sensitivity analyses

One-way sensitivity analyses for selected variables in the base case are reported in section 6.3.3.1 of the MS. The results of probabilistic sensitivity analysis (PSA) are reported in the MS section 6.3.3.2. The MS tables 6.16 and 6.18 present a range of estimates of the probabilities of entecavir being cost-effective under the assumptions of the various threshold values for HBeAg

positive and HBeAg negative populations respectively. The means and measures of variation of costs and outcomes in the HBeAg positive population are reported in the MS Table 6.17. The MS Figures 6.5 and 6.6 show the cost-effectiveness acceptability curves (CEACs) for entecavir vs comparators pegylated interferon alpha 2a, lamivudine and telbivudine for HBeAg positive and HBeAg negative populations respectively.

4.2.7 Model validation

Approaches to validating the model are described in the MS section 6.2.14, p.133. The principal validation of the model structure and key clinical assumptions appears to have been an opinion expressed by "expert clinical hepatologists and gastroenterologists". The mathematical logic and statistical calculations appear to have been reviewed by an independent statistician and a modeller not involved in the development or analyses (though no further detail is given on the scope of this or the clinicians' review nor the criteria used to establish the model's validity).

The approach to establishing external consistency was to compare the model inputs and results with the published evaluations reviewed in section 6.1.2 of the MS.

4.2.8 Results

Consistent with the NICE reference case, results from the base case economic model are presented as incremental cost per QALY gained. For each treatment group, drug costs for the duration of treatment (two years in the HBeAg positive model and five years in the HBeAg negative model except for pegylated interferon alpha 2a, which is administered for one year in both models) are reported separately from other healthcare costs and the total lifetime costs along with the lifetime QALY gains. The results are presented in the MS Tables 6.11-6.13 for HBeAg positive, HBeAg negative populations and the population of lamivudine-refractory patients respectively. The PSA gives 95% CIs for both costs and QALYs estimated in the HBeAg positive disease model (the MS Table 6.17). The PSA of the results of the modelled economic evaluation of entecavir in HBeAg negative population were not reported and needed to be estimated by the ERG.

Table 21, Table 22 and Table 23 below summarise the results reported in Tables 6.11-6.13 and 6.17 of the MS.

Table 21 Cost effectiveness results for entecavir as first-line antiviral therapy in HBeAg-positive patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)	Total cost (deterministic)	Total mean cost (PSA)(95%CI)	ICER* (deterministic)

Entecavir	16.84	16.96 (15.42, 18.28)	£23,095	£22,705 (£19,212, £26,906)	N/A
Lamivudine	16.61	16.75 (15.44, 17.88)	£19,784	£19,506 (£16,672, £22,834)	£14,329
Peg IFN	16.64	16.75 (15.51, 17.83)	£21,396	£21,343 (£18,929, £24,136)	£8,403
Telbivudine	16.84	16.97 (15.65, 18.15)	£22,858	£22,858 (£18,109, £25,702)	Telbivudine dominant

Peg IFN=pegylated interferon alpha 2a; PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio. N/A=not applicable
*The ICER values are calculated as follows: firstly, the incremental total cost of entecavir vs a comparator is calculated and secondly, the result is divided over the incremental benefit of entecavir vs the same comparator.

Table 22 Cost effectiveness results for entecavir as first-line antiviral therapy in HBeAg-negative patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)*	Total cost (deterministic)	Total mean cost (PSA)(95%CI)*	ICER** (deterministic)
Entecavir	14.41	14.34 (12.96, 15.68)	£38,449	£38,740 (£34,837 £43,083)	N/A
Lamivudine	13.80	13.89 (12.46 15.24)	£30,270	£30,304 (£26,343, £34,756)	£13,208
Peg IFN	13.71	13.52 (12.10, 14.92)	£33,142	£33,926 (£30,021, £38,443)	£7,511
Telbivudine	14.21	14.30 (12.91, 15.61)	£37,028	£37,034 (£33,085, £41,456)	£6,907

Peg IFN=pegylated interferon alpha 2a; PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio; N/A=not applicable
*Not reported in the MS. The ERG has obtained the estimates by running a set of PSAs for each of the comparators.
** The ICER values are calculated as follows: firstly, the incremental total cost of entecavir vs a comparator is calculated and secondly, the result is divided over the incremental benefit of entecavir vs the same comparator.

Table 23 Cost effectiveness results for entecavir as salvage therapy in HBeAg-positive patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)*	Total cost (deterministic)	Total mean cost (PSA)(95%CI)*	ICER (deterministic)
Entecavir	16.43	16.42 (15.15, 17.55)	£25,114	£25,525 (£22,730 £28,770)	N/A
Adefovir/ Lamivudine	16.36	16.40 (15.16 17.50)	£26,116	£26,233 (£23,537, £29,258)	Entecavir dominant

PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio; N/A=not applicable
*Not reported in the MS. The ERG has obtained the estimates by running a PSA.

The MS summarises the results for the base case analysis stating on p.20 that entecavir is a cost effective first-line antiviral therapy in nucleoside naïve HBeAg-positive and -negative

patients with an incremental cost per additional QALY of £14,329 and £13,208, respectively when compared to lamivudine. In the analysis versus pegylated interferon alpha 2a, entecavir demonstrated cost-effectiveness with an incremental cost per additional QALY of £8,403 and £7,511 in HBeAg positive and HBeAg negative patients respectively. The MS stated on p.20 that in HBeAg positive patients, telbivudine and entecavir have similar efficacy with small difference in costs (telbivudine showing a slightly lower cost of £187 versus entecavir over a lifetime horizon). This suggests that in the base case analysis telbivudine is a dominant treatment choice in this sub-group of patients, although the PSA demonstrates that entecavir and telbivudine are comparable in this patient population. In HBeAg negative patients, entecavir was cost effective compared with telbivudine with an incremental cost per additional QALY of £6,907.

In the population of lamivudine-refractory HBeAg positive patients, comparison of entecavir with the adefovir/lamivudine combination showed that entecavir was the dominant strategy. The MS stated on p.20 that this analysis should be treated with caution due to the paucity of data in the HBeAg positive lamivudine-refractory population. A PSA for this sub-group of CHB patients does not seem to have been conducted/presented.

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 24 below, drawn from common checklists for economic evaluation methods (e.g. Drummond *et al*, 1997).

Table 24 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	On page 105 the MS states that the primary aim of this economic evaluation is to estimate the cost-effectiveness of entecavir as the first-line antiviral treatment for CHB in both HBeAg-positive and -negative patients. The entecavir dose of 0.5 mg once daily is used in these patients (p.129 of the MS). The MS states that the secondary aim is to estimate the cost-effectiveness of entecavir in patients who have failed

		prior lamivudine therapy. The entecavir dose of 1.0 mg once daily is used in these patients (p.129 of the MS).
Is there a clear description of alternatives?	Yes	The MS states (p.105) that in both HBeAg-positive and -negative patients the relevant comparators for the first-line treatment for CHB are lamivudine, telbivudine and pegylated interferon alpha 2a. The MS states that the relevant comparator in patients who have failed prior lamivudine therapy is a combination of lamivudine and adefovir.
Has the correct patient group / population of interest been clearly stated?	Yes	The population of patients is correctly identified on p.106 of the MS as adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation). The cost-effectiveness analyses of CHB treatment alternatives are reasonably conducted with respect to the sub-groups of nucleoside naïve HBeAg-positive and -negative patients and lamivudine-refractory patients.
Is the correct comparator used?	Yes	The comparators are as specified in the decision problem outlined in section 2 of the MS. section 6.2.10.1 specifies the doses for different sub-groups of CHB patients In nucleoside naïve HBeAg-positive and -negative patients the comparators and the corresponding doses are: Telbivudine 600 mg once daily; Lamivudine 100 mg once daily; Pegylated interferon alpha 2a 180 mg injection once weekly. In patients who have failed prior lamivudine therapy the dose of salvage combination therapy of lamivudine and adefovir is lamivudine 100 mg plus adefovir 10 mg once daily
Is the study type reasonable?	Yes	Cost-utility analysis is reasonable, as the major effects of successful treatment of CHB would be expected to be a reduction in mortality due to preventing further progression of liver disease and an improved quality of life.
Is the perspective of the analysis clearly stated?	Yes?	The MS states on p.108 that “the perspective of the model is the NHS and PSS, reflecting the reference case”. Also on p.20, and p.105 the MS states that the perspective of the economic evaluation is “restricted to the UK NHS and PSS and the cost-base year is 2006”. However on p.131 of the MS states that “health state costs were inflated to their 2007 price year equivalents”. The drug costs are taken from the 2007 BNF. This indicates that the base year to which costs relate is 2007 rather than 2006.
Is the perspective employed appropriate?	Yes	The MS states in section 6.2.5 that the perspective of economic evaluation is the NHS and PSS. However, it does not seem that the PSS resources/outcomes are included. As major differences between treatment groups are expected to be related to management of progression through the stages of CHB then concentration on NHS rather than PSS is appropriate. The MS states on p.108 that this perspective “potentially undervalues the therapeutic benefits and therefore the cost-effectiveness of entecavir, as patient benefits such as the ability to continue working, increased work productivity and reduced negative psychological and social symptoms due to CHB condition are excluded”. It is reasonable to suggest that

		the alleged increase in work productivity is not captured within the NICE framework, however it is likely that to some degree the treatment effect in terms of improvement in psychological and social symptoms is reflected in different estimates of the utility weights used in the model (see Table 1, Levy *et al* 2007[36])
Is effectiveness of the intervention established?	Response to treatment – Yes?	In nucleoside naïve HBeAg-positive and -negative patients the estimates of clinical effectiveness (i.e. seroconversion and suppression of HBV DNA replication respectively) were derived from the fixed effects multiple treatment comparison described in section 5.6 of the MS and Appendix 8.4. See section 3.1.5 of this report for an appraisal of the methods used.
	Cirrhosis risk reduction- Yes?	In nucleoside naïve HBeAg-positive and lamivudine-refractory patients, estimates of the reduction of risk of cirrhosis were derived from the REVEAL-HBV prospective cohort study (Iloeje *et al*, 2006)[9] in combination with viral suppression data from the network meta-analysis and published clinical trials [12 28 31 27 15 5]. Concerns are raised about validity, reliability and appropriateness of the estimates of relative risk of cirrhosis described in section 6.2.8.2 of the MS. See section 4.4.1.2 for details.
	Resistance rates- No	Estimates of the differential risks of developing resistance to active treatment came from various sources of evidence, including RCTs, open-label extensions of RCT and observational studies. These are listed in Table 6.4 and in section 6.2.8.2 of the MS. Studies other than open-label extensions of RCTs described in section 5.8 were not assessed for methodological quality. The MS states on p.86, that a formal network meta-analysis of resistance rates was not possible because the data came from non-RCTs and the patient populations were too heterogeneous. It is therefore impossible to establish the magnitude of the differences in resistance rates between the treatment groups with statistical certainty.
	No	In lamivudine-refractory patients, estimates of clinical effectiveness were derived from the simple descriptive analysis of data reported in 3 RCTs presented in Table 5.14 of the MS which was presented as an indirect comparison. It is impossible to establish the magnitude of the differences in resistance rates between the treatment groups with statistical certainty.
Has a lifetime horizon been used for analysis?	Yes	The clinical effectiveness data were only available for the short term and a model was required to extrapolate the treatment effects to the life time horizon, as is appropriate for the chronic nature of the disease. The model includes 100 cycles (i.e. 100 years).
Are the costs and consequences consistent with the perspective employed?	Yes	The model seems to have included only NHS resource use. Cost estimates are consistent with the NHS perspective. Consequences are presented as QALYs, consistent with the model perspective
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year

Is incremental analysis performed?	Yes	ICERs from deterministic analysis are presented in Tables 6.11-6.13 for the base case in nucleoside naïve HBeAg-positive, HBeAg-negative and lamivudine-refractory patients respectively.
Is sensitivity analysis undertaken and presented clearly?	Yes	All variables were subject to one-way sensitivity analysis. Results of one-way sensitivity analysis of the key variables that had the greatest impact on the variability on the incremental cost/QALY results are clearly presented in Tables 6.14 and 6.15 of the MS for HBeAg-positive and -negative patients respectively. Results of probabilistic sensitivity analysis are presented in Tables 6.16 and 6.18 of the MS report for HBeAg positive and HBeAg negative populations respectively. The PSA produced a range of estimates of the probabilities of entecavir being cost effective under the assumptions of the various threshold values and for each of the comparator treatments. Tables 6.16 and 6.18 also present estimates of the probabilities of entecavir being dominant over the comparator and visa versa. MS figures 6.5 and 6.6 show the CEACs for entecavir vs comparators pegylated interferon alpha 2a, lamivudine and telbivudine for HBeAg positive and HBeAg negative populations respectively.

NICE reference case

Table 25 NICE reference case requirements

NICE reference case requirements	Included in Submission
Decision problem: As per the scope developed by NICE	Yes
Comparator: Alternative therapies routinely used in the UK NHS	Yes[a]
Perspective on costs: NHS and PSS	Yes[b]
Perspective on outcomes: All health effects on individuals	Yes
Type of economic evaluation: Cost effectiveness analysis	Yes
Synthesis of evidence on outcomes: Based on a systematic review	Yes/No[c]
Measure of health benefits: QALYs	Yes
Description of health states for QALY calculations: Use of published utility values obtained with a standardised and validated generic instrument	Yes[d]
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes[e]
Source of preference data: Representative sample of the public	Uncertain[f]
Discount rate: 3.5% pa for costs and health effects	Yes

a. The comparators are: pegylated interferon alpha 2a, lamivudine, telbivudine. Appraisal of the sequential use of antiviral drugs and combination therapy, which is mentioned in the reference case, is limited to the separate sub-group analysis of lamivudine-refractory patients and to the inclusion of a combination of adefovir with an active treatment for patients developing resistance to the initial treatment in the HBeAg positive- and HBeAg negative- disease models.
b. Costs are NHS only
c. Systematic review and the fixed effects multiple treatment comparison have produced estimates of treatment response in terms of rates of seroconversion and suppression of HBV DNA replication for HBeAg-positive and HBeAg-negative nucleoside naïve patients respectively. No systematic review and evidence synthesis undertaken to estimate seroconversion rates in lamivudine-refractory patients. A systematic review and evidence synthesis was undertaken to estimate resistance rates in nucleoside naïve patients in entecavir treatment. However no systematic review of clinical evidence was conducted in relation to the comparators.

d. EQ-5D utility values for the UK population aged 35-44 years were applied to the health states corresponding to HBeAg Seroconversion and HBsAg loss. e. Use of published utility values estimated with a HRQoL instrument specifically designed for CHB (i.e. health states correspond to natural disease progression as assumed in the model) using the standard gamble method (Levy et al, 2007[36]). f. Although the study by Levy et al (2007)[36] involves a representative sample of the population from six countries, the utility values used in the model are obtained from 100 uninfected individuals residing in the UK. It is uncertain whether the sample used to elicit utility values is representative of the UK population.

N/A=not applicable

4.4 Modelling methods

An outline critical review of modelling methods has been undertaken. The review has used the framework for good practice in modelling presented by Philips *et al* (2004)[43] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The MS presents two Markov models for the HBeAg positive and HBeAg negative variants of the disease. The models are written in Microsoft Excel and are fully executable. Inputs changed in the *'Inputs'* worksheet produce immediate changes in the results worksheet. Use of a Markov model is appropriate for chronic disease conditions such as CHB.

The MS presents schematics for the HBeAg positive and HBeAg negative disease models in Figure 6.3 and Figure 6.4 respectively. These are reproduced in

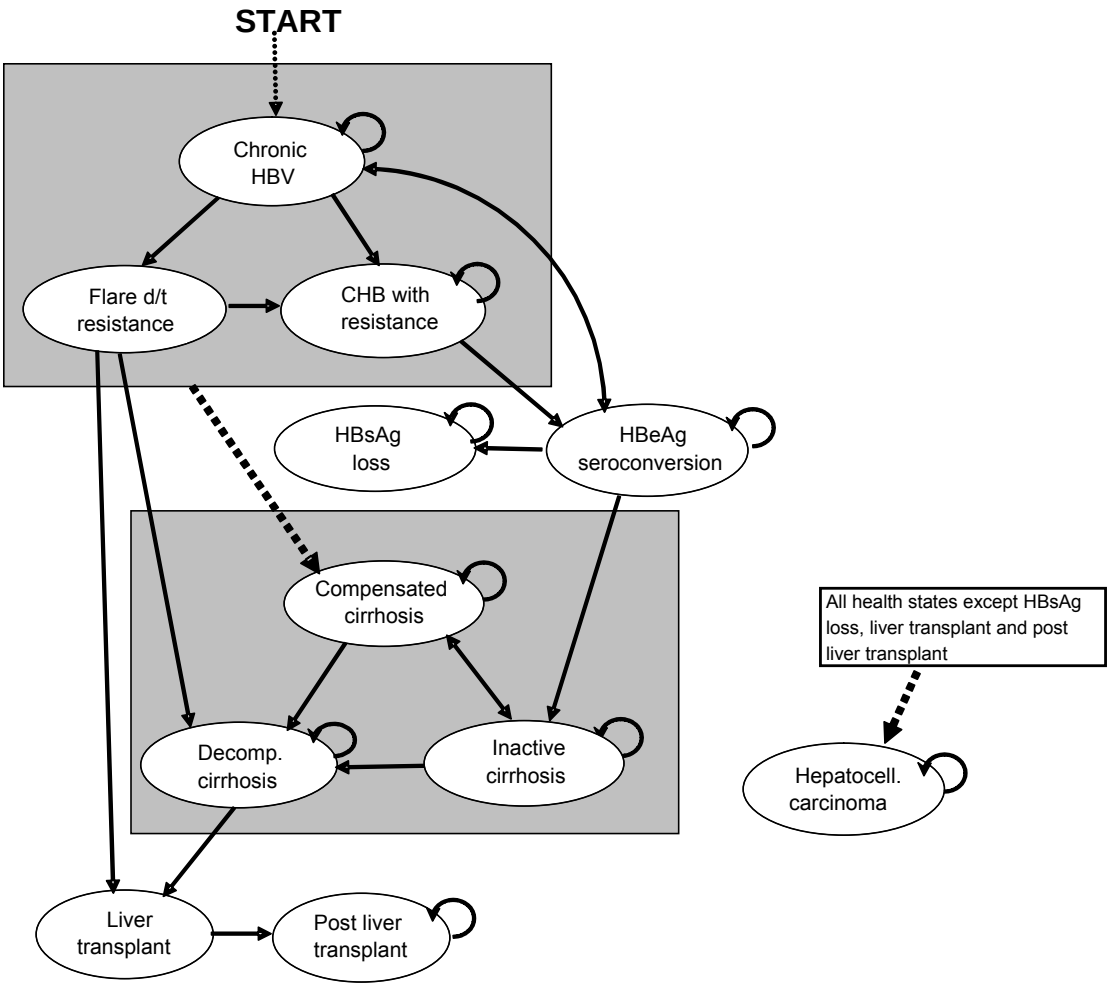
Figure 1 and

Figure 2 below. However, the schematic representations do not reflect the complexity of the models as these do not outline all the health states and all transitions. A more complete schematic of the HBeAg negative disease model only is available in the Excel spreadsheet. The inputs for the model are shown in the MS in Tables 6.3-6.5. The list of inputs is incomplete. In particular, out of six transition probabilities relating to the "Flare d/t resistance" health state (where d/t = due to), Table 6.3 shows only two, although a footnote explains how the transition probability from CHB to "Flare d/t resistance" was derived.

Figure 1 depicts the HBeAg positive disease model, which includes 14 health states although only 11 are depicted (CHB, HBeAg seroconversion, HBsAg loss, resistance, flare,

compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation).

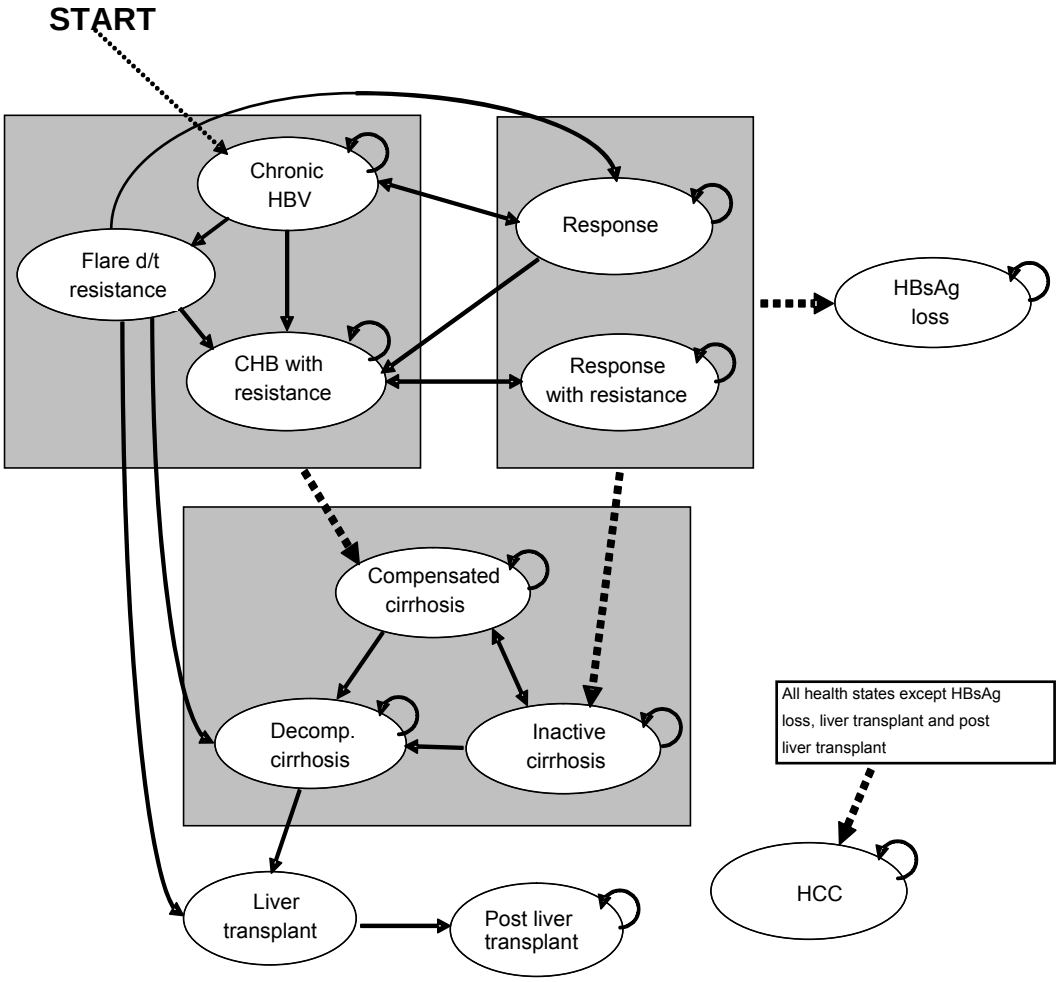
Figure 1 Schematic of the HBeAg positive disease model (reproduced from Figure 6.3 in the MS)



Both models assume complex dynamics between treatment, response and resistance to treatment. In particular, patients can achieve a response to initial treatment as well as a response to the salvage therapy prescribed to patients who subsequently develop resistance to the initial treatment. In the HBeAg negative disease model these treatment pathways are reflected in two health states representing the response to treatments (response to the initial treatment and response to the salvage therapy). Response to either the initial or the salvage

treatment may be followed by virological breakthrough resulting in the loss of response. These pathways are depicted by the arrows connecting response states with the "CHB with resistance" health state.

Figure 2 Schematic of the HBeAg negative disease model (reproduced from Figure 6.4 in the MS)



The MS does not provide a justification for the differences in the structures of the HBeAg positive and HBeAg negative disease models. In particular, the need for introducing two health states representing response in the HBeAg negative disease model (i.e. "Response" and "Response with resistance", which is likely to be interpreted as "Response to salvage treatment"

(Figure 6.4 of the MS)) instead of a single "Response" state as in the HBeAg positive disease model was not explained.

Overall, the structure of the model is not dissimilar to those used in published economic evaluations (Shepherd *et al*, 2006[7], Veenstra *et al*, 2007 [25], Kanwal *et al*, 2005 [44]) and can be viewed as corresponding to the natural progression of the disease. However, the ERG raised a few concerns discussed below. Notwithstanding these concerns, the modelling approach and health states used in the model seem reasonable to the ERG.

4.4.1.1 Structural Assumptions

The MS indicated that a key clinical event in both models is the progression from CHB to "active" cirrhosis (this is also referred to, rather confusingly, as "compensated" cirrhosis, which can be both active and inactive.) The "inactive" cirrhosis state is occasionally referred to as a "non-replicating" state. This inconsistent labelling of the same health states has unnecessarily complicated understanding of the model. The MS provided only a partial explanation of the model schematic. In particular, the clinical rationale for including inactive in addition to compensated cirrhosis was not explained, although some clarification was provided upon request (see Appendix 1, B2-B3).

Inclusion of three different cirrhotic health states: active, inactive and decompensated, is a special feature of both models presented in the MS. The economic evaluations reviewed in section 6.1.2 of the MS conventionally include only two cirrhotic states: compensated and decompensated cirrhosis. However, a model structure, identical to the one in the MS, was recently published in a Bristol Myers Squibb funded economic evaluation of entecavir versus lamivudine with adefovir salvage in HBeAg positive patients (Veenstra *et al*, 2007[25]). The publication appeared after the manufacturer submitted that model to NICE and was not assessed in the MS.

One of the structural assumptions made in both models is that patients with response (defined either as seroconversion in the HBeAg positive disease model or viral suppression in the HBeAg negative disease model) cannot enter the state of active cirrhosis other than first entering the state of inactive cirrhosis. This assumption differs from those in previously published economic evaluations (Shepherd *et al*, 2006 [7], Veenstra *et al*, 2007[25]) where patients

with a response are assumed to have a positive, although fairly small (1%), risk of developing active/compensated cirrhosis. On the other hand, it was assumed in Kanwal *et al*, (2005)[44] (one of the cost-effectiveness studies included in the manufacturer's systematic review, see MS section 6.1) that patients with response have low rates of progression to cirrhosis (0%-0.5%) (p.W192). According to the model assumptions, inactive cirrhosis is associated with a significantly lower risk of decompensation than active cirrhosis (i.e. 0.8% vs 5%, Table 6.3 of the MS). The value of transition probability of 0.8% from inactive cirrhosis to decompensated cirrhosis was obtained from the study by Fattovich *et al* (2002)[45].

The ERG was concerned about the epidemiological data that were used to derive this probability. In response to the ERG request, clarification was received from the manufacturer stating that although the rates of decompensation were not reported separately for active and inactive cirrhotic patients in Fattovich *et al* (2002)[45], the study found that the risk of hepatic decompensation in patients with positive HBV-DNA (active cirrhosis) compared with patients with negative HBV-DNA (inactive cirrhosis) was approximately four-fold higher. This ratio was then used to convert the annualised rate of decompensation (3.1%) into the 0.8% transition probability from inactive to decompensated cirrhosis (see Appendix 1, B3). Contrary to this assertion, the ERG clinical expert felt that in patients with inactive (non-replicating) cirrhosis no further liver damage is occurring and transition from inactive cirrhosis to decompensated cirrhosis will not occur. Although the ERG has not undertaken the comprehensive validation of the underlying clinical evidence used to derive the model probability values, it is felt that the MS might have misinterpreted the results reported in Fattovich *et al* (2002)[45]. The estimate of the relative risk of decompensation in Fattovich *et al* (2002)[45] over the observation period with the median of 6.6 years seems to have been obtained while controlling for the HBV-DNA status at entry (p.2891). Some of the patients with non-replicating HBV-DNA status at baseline might still develop decompensated cirrhosis at some point during the observation period, however these patients need to become HBV-DNA-positive first (i.e. move from the inactive/non-replicating cirrhosis health state). This is consistent with the manufacturer's reply to the ERG request for clarification, which (stated that "patients with inactive disease are not likely to become cirrhotic with inflammatory response without first seroreverting or becoming HBV DNA positive" (See Appendix 1, B2). This view seems to be inconsistent with another assumption of the model which sets the value of the transition probability from inactive cirrhosis to HCC equal to the transition probability from active cirrhosis to HCC. The MS provided no clinical rationale for this assumption.

In both models patients with a response (defined either as HBeAg seroconversion in HBeAg positive patients or as an undetectable viral load in HBeAg negative patients) could enter the active/compensated cirrhosis state only via the inactive cirrhosis health state. In comparison, the previously published economic evaluations (Shepherd *et al*, 2006[7], Veenstra *et al*, 2007[25]) assumed that one percent of patients with a response can develop compensated cirrhosis. This estimate is 10 times higher than the risk of developing inactive cirrhosis in patients with a response which is estimated at 0.1% in the model. The MS indicated that this transition probability was taken from the study by Hsu *et al* (2002)[46]. In their reply to the ERG request for justification the manufacturer stated that the inactive cirrhosis state "has relatively little impact on the results of the analyses. For example, the transition probability from response/seroconversion to the inactive cirrhosis state is 0.1%; increasing this estimate by even 10-fold has little effect" (Appendix 1. B2). Although this statement is correct, the problem is not restricted to the differences in risk estimates. More important is the difference in structural assumptions, where, through the introduction of the inactive cirrhosis state, the MS model artificially slows progression of patients with response to the more advanced stages of liver disease taking an additional advantage of the differential treatment effect in the HBeAg negative model. The impact of this assumption on the results of the cost-effectiveness analysis is unclear.

The MS states on p.109 that patients could also develop antiviral drug resistance with or without a severe hepatic flare (defined as ALT>10 x upper limit of normal). No further clinical justification for introducing the "Flare due to resistance" health state was provided. In their reply to the ERG request for justification the manufacturer stated that all patients who experienced resistance should have a risk of severe flare and that the average rate of severe flare for patients with resistance across five years is approximately 2-3% per year (Lok *et al*, 2003[32]) (Appendix 1, B1(b)). Interventions without resistance (at all, or in earlier years) will not have patients moving from CHB to "Flare due to resistance" (see Appendix 1, B1(e)).
According to the model structure, patients treated for CHB can develop "Flare due to resistance" followed by transitioning to the "CHB with resistance" and receiving salvage therapy.
It remains unclear, whether:

- The direction of patient transition between the states is consistent with the course of disease. The model assumes that flares are followed by patients moving to the resistance

state, while the clarifications received from the manufacturer suggest the opposite, that patients who experienced resistance should have a risk of severe flare;

- The cycle length of one year is consistent with the average duration of flares.

In the model the annual probability of developing a severe flare (presumed to be associated with resistance) was multiplied by the probability of developing resistance to treatment. It is implicitly assumed that the treatment groups that have a reduced risk of resistance are at a lesser risk of developing “Flares due to resistance” and subsequently experiencing HCC, decompensation, and/or liver transplant. The “Flare due to resistance” health state seems to be introduced into the models to take an additional advantage of the differences in risk of developing resistance to nucleosides between the treatment groups. The effect of the modelling assumptions associated with the “Flare due to resistance” health state were tested in the ERG sensitivity analysis by assigning zero probability to the risk of experiencing “Flare due to resistance”. See section 4.4.1.5.

In the base case scenario patients are treated for two years in the HBeAg positive disease model and for five years in the HBeAg negative disease model. The duration of treatment assumed in the models is poorly justified. However, the MS also provided a scenario analysis where HBeAg negative patients receive lifetime treatment. The ERG clinical experts felt that for the majority of patients the treatment lasts longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models, respectively and that the lifetime treatment scenario for the HBeAg negative disease is the most appropriate model. The ERG explored the impact of longer treatment duration for HBeAg positive patients in scenario analysis (section 4.4.1.4)

In the MS model, only pre-cirrhotic patients receive treatment (i.e. once the patients transit to the active cirrhosis state, the treatment is terminated). However, the ERG clinical expert reviewer felt that patients who progress to the compensated cirrhosis state do not cease treatment (entecavir is not indicated for the patients with decompensated cirrhosis). Another assumption of the model is that all patients start in the CHB health state, however in practice a certain proportion of patients may first present at the stage of compensated cirrhosis. These issues are explored in the ERG sensitivity analysis (see section 4.4.1.4)

4.4.1.2 Data Inputs

Patient Groups

The cohort of HBeAg positive patients enters the Markov state transition model (HBeAg positive disease model) at 35 years of age. The patients are HBV DNA and HBeAg positive, non-cirrhotic, with elevated liver enzymes (ALT), nucleoside naïve and had received no prior CHB therapy for at least six months. The cohort of HBeAg negative patients enters the Markov state transition model (HBeAg negative disease model) at 44 years of age. The patients are HBV DNA and HBeAg-positive, non-cirrhotic, with elevated liver enzymes (ALT), nucleoside naïve and had received no prior CHB therapy for at least six months. The cohort of HBeAg positive lamivudine-resistant patients is similar to the cohort of HBeAg positive patients except that they are no longer nucleoside naïve.

The characteristics of the model populations are generally consistent with the MS decision problem, where the population is described as adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation). However, the decision problem does not limit the CHB populations to the sub-group of non-cirrhotic patients. The assumption of the patients being non-cirrhotic at baseline does not seem to be observed in real clinical practice where a certain proportion of patients (reported to be up 10% in the entecavir RCTs systematically reviewed by the manufacturer, see MS section 5.2) present with compensated cirrhosis. In particular, HBeAg-negative patients tend to be older and have a more advanced liver disease (Lok & McMahon, 2007[47]). Therefore the populations used in the model does not completely represent those observed in practice. The model results are sensitive to the proportion of patients with compensated cirrhosis at baseline. This is explored in the ERG scenario analysis (see section 4.4.1.4 below).

Clinical Effectiveness

The MS assumes that untreated HBeAg negative patients do not achieve a spontaneous response in terms of viral load suppression, although spontaneous HBsAg loss is possible. The MS provides no clinical justification for this assumption.

The MS also assumes that 30% of HBeAg negative patients who had received antiviral treatment for five years may achieve a response (an undetectable viral load) after the treatment

termination. A small follow-up study of adefovir treated patients is quoted to support this assumption (Hadziyannis *et al*, 2006)[48]. The ERG clinical expert reviewer felt that extrapolating results of the small study of adefovir treated patients across other treatment groups creates a source of uncertainty. The ERG undertook a scenario analysis to explore the effects of different estimates of the treatment durability (see section 4.4.1.4 below).

Clinical effectiveness inputs in the model relate to the:

- HBeAg seroconversion rates in the HBeAg positive population;
- Rates of achieving an undetectable viral load as a primary clinical outcome in the HBeAg negative population, although this outcome is also included in the HBeAg positive disease model in terms of differential risks of developing compensated/active cirrhosis; and
- Risk of developing resistance to active treatment;
- HBsAg loss.

A network meta-analysis (the MTC) was undertaken to obtain the estimates of response rates in nucleoside naïve patients (HBeAg seroconversion rates in the HBeAg positive population and undetected viral load in HBeAg negative population). The response rates in the first year of treatment estimated by the MTC were used as transition probabilities in the model. The ERG considers that due to the issues raised in section 3.1.5 of this report the results of the MTC are uncertain and should be interpreted with caution. It appears, however, that the outcomes of the MTC for the first year of entecavir vs lamivudine are consistent with the results reported in the large RCTs presented in the manufacturer's systematic review of clinical effectiveness (Studies 022, 023, 027).

The MS reported the MTC estimates of clinical effectiveness results in year two (the MS Tables 5.11 and 5.13) as cumulative rather than annual values. Regardless of the methodological quality of the MTC, these results could not be used in the model. The probabilities of response in year two were derived specifically for the purposes of the Markov model. However, the method for calculating the probabilities is poorly explained in the footnote to MS Tables 6.4 and 6.5 of the MS for the HBeAg positive population and the HBeAg negative population respectively. The ERG was unable to validate the second year probabilities of response since the denominator of the formulae used for calculating response rates is the "proportion of patients who go on to year two", which was not reported in the MS (see footnotes to the MS Tables 6.4 and 6.5). It is not clear what basis for calculating the proportion of patients who

continue treatment in the second year was used (i.e. all randomised patients, treated patients, patients who completed the first year, etc.).

It appears that the average number of 82% of patients who continue treatment into the second year is used across all treatment groups in the HBeAg positive population. If this is correct, the estimated 82% of patients may be an overestimate of the proportion of patients retained in treatment after the first year (see the MS flow charts 5.3.3.2-5.3.3.4 for comparison). Also the use of an average across the groups implicitly assumes that the dropout rates across the treatment groups are independent of treatment effectiveness. This assumption does not seem to be reasonable. For example, a conservative assumption of the year two retention rates being 74% in entecavir and 59% in lamivudine (based on the Study 022 retention rate in year two calculated from the MS flow chart 5.3.3.1, page 52) would produce year two HBeAg seroconversion rates of 11.5% and 14.4% in entecavir and lamivudine groups respectively. The latter is two times higher than the clinical effectiveness rate of 7.2% reported in the MS Table 6.4.

The ERG concludes that

- methods of deriving the year two estimates of response to treatment are not clearly explained or justified;
- the estimates of response rates used in the model may bias the cost-effectiveness results in favour of entecavir.

The estimates of the risks of developing resistance to active treatment came from published clinical trials (Lai *et al*, 2005 [27], Lau *et al*, 2005[28], Marcellin *et al*, 2004[29]), open-label extensions of RCTs (Lee *et al*,2006[30], Han *et al*, 2007[31]), unpublished entecavir clinical study reports (CSR[13 18 22]) and observational studies (Lok *et al*, 2003[32], Di Marco *et al*, 2004[33]). The ERG has not undertaken a systematic cross-checking of publications used to obtain the values of transition probabilities. A systematic review of the studies reporting resistance rates associated with any of the comparator drugs does not seem to have been undertaken. The sources of clinical evidence employed to derive transition probabilities presented in section 5.6.6 of the MS do not seem to fully correspond to the sources of the clinical evidence presented in the MS Tables 6.4 and 6.5. The MS does not provide a complete assessment of the methodological quality of the clinical evidence from which these estimates of transition probabilities were extracted.

The estimates of clinical effectiveness of entecavir treatment (HBeAg seroconversion rates, resistance rates and risk of developing compensated cirrhosis) in HBeAg positive lamivudine–refractory patients were obtained from the journal publication for Study 026 (Sherman *et al* 2006)[15], plus unpublished entecavir clinical study reports (CSR[16 22]) for the entecavir treatment group. For the comparator, adefovir and lamivudine combination therapy, various published sources were employed (Perrillo *et al*. 2004[5] and Peters *et al*. 2006[6], Buti *et al*, 2007[34], Hsu *et al*, 2002[46]). As discussed in section 3.1.5 of this report, very little can be reliably concluded about the relative efficacy of the two interventions, therefore the outcomes of the cost-effectiveness analysis are uncertain.

Calculations of the estimates of the between-group difference in the risk of developing active/compensated cirrhosis in patients who did not achieve HBeAg seroconversion but nevertheless responded to treatment in terms of viral load suppression in the HBeAg positive disease model are explained in MS section 6.2.8.2. This differential effect of treatment is assumed to occur only in the first year of treatment (footnote d, Table 6.4 of the MS). This additional differential treatment effect was not discussed in the sections on clinical effectiveness in the MS. The probability estimates are based on the relationship between the viral load and the risk of cirrhosis elicited from a single prospective, population-based cohort study of untreated Taiwanese individuals with CHB (the REVEAL study)[9]. The MS does not provide a sufficient justification of the relevance of this evidence to the UK population treated for CHB. The average viral load values are extracted from various studies that were not systematically reviewed and assessed for quality (Lau *et al*, 2005[28], Han *et al*, 2007[31], Lai *et al*, 2005[27]).

Patient outcomes

The MS models assume that health states corresponding to the stages of natural disease progression (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) determine the patients' quality of life. This is consistent with approaches used in the previously published economic evaluations of CHB treatments (Wong *et al*, 1995[35], Veestra *et al*, 2007[25], Shepherd *et al*, 2006[7]).

Utility values were obtained from the recent study by Levy *et al* (2007)[36]. In this study standard gamble utilities were elicited using an interviewer-administered survey from populations in six

countries with a total number of 534 CHB-infected patients and a total number of 600 uninfected respondents. Utility values were obtained in relation to six CHB states: CHB, compensated cirrhosis, decompensated cirrhosis, liver transplantation, post-liver transplantation and HCC.

The age-sex adjusted utility values elicited from 100 uninfected respondents in the UK were used in the model. Although the study by Levy *et al* (2007)[36] involves a representative sample of the population from six countries, the utility values used in the model are from 100 uninfected individuals residing in the UK. It is uncertain whether the sample used to elicit utility values used in the model is representative of the UK population.

Levy *et al* (2007)[36] observed that uninfected respondents had higher mean utility values than infected respondents for most of the health states. The MS appropriately used the higher values in order to obtain the more conservative estimates of QALYs.

Utility values for HBeAg seroconversion, HBsAg loss or response states were not elicited as part of the utility study by Levy *et al*, (2007)[36]. The MS assumed these values to be no different to those of a normal individual, so the UK published tariffs on the five-dimensional European Quality of Life scale (EQ-5D) for individuals aged 35–44 years (Kind *et al*, 1999[49]) were applied to these states. The MS commented that this is consistent with utility assumptions made by Shepherd *et al* (2006)[7] for NICE TA964 (p.128 of the MS).

However, utility values in Shepherd *et al* (2006)[7] were obtained by applying the decrements, specific to each of the CHB health states to the population norms reported in Table A of Kind *et al* (1999)[49]. For example, patients in the CHB health state were assigned a decrement of 0.04 (i.e. a baseline value of 0.93 for the uninfected 31 year old individual was reduced by 0.04 to obtain the value of 0.89 which is similar to the value of 0.88 used in the model).

In the MS models the cohort of HBeAg positive patients is younger at baseline (35 years old) than the cohort of HBeAg negative patients (44 years old). There is also an age difference at baseline between the cohort of HBeAg positive patients in Shepherd *et al*, (2006)[7] (mean age 31 years) and the cohort of HBeAg negative patients (mean age 40 years). Appropriately, different baseline age-related population norms were used in these two cohorts in the model reported in Shepherd *et al*, (2006)[7]. On the contrary, age differences have not been translated in the differences in utility values used in HBeAg positive and HBeAg negative models in the

MS; the same fixed utility values were applied to each health state in the MS model regardless of the underlying age of the cohort. The approach used in Shepherd *et al* (2006)[7] seems to be more reasonable. Table 26 presents the baseline values used in the MS model and in Shepherd *et al*. (2006)[7].

Table 26 Utility values assigned to the CHB patients in different health states as reported in the MS model and in Shepherd *et al*, 2006[7]

Health state (source of the utility value estimate)	Utility values used in the MS model (Table 6.9 of the MS)	Utility values at the baseline used in the HBeAg+ve model in Shepherd *et al* (2006 p.88)	Utility values at the baseline used in the HBeAg-ve model in Shepherd *et al* (2006 p.88)
CHB (Levy *et al*, 2007)[36]	0.88	0.89	0.87
Seroconversion/Response (assumed to be equal to the population norm)	0.91	0.93	0.91
HBsAg Seroconversion (assumed to be equal to the population norm)	0.91	0.93	0.91
Flare due to resistance (assumption in the MS)	0.36	Not included in the model	Not included in the model
Resistance to treatment (assumption in the MS)	0.88	Not included in the model	Not included in the model
Active/compensated cirrhosis (Levy *et al*, 2007)[36]	0.87	0.49	0.47
Inactive cirrhosis (assumption in the MS)	0.88	Not included in the model	Not included in the model
Decompensated cirrhosis (Levy *et al*, 2007)[36]	0.36	0.39	0.37
Hepatocellular carcinoma (Levy *et al*, 2007)[36]	0.42	0.39	0.37
Liver transplant (Levy *et al*, 2007)[36]	0.69	0.38	0.36
Post-Liver transplant (Levy *et al*, 2007)[36]	0.82	0.61	0.59
Adverse events from pegIFN treatment (Veenstra *et al* 2007)[25]	0.05	Not included in the model	Not included in the model

Peg IFN =pegylated interferon alpha 2a; HBeAg+ve = HBeAg positive; HBeAg-ve = HBeAg negative;

The utility weights used in the MS models in application to the compensated cirrhosis state, liver transplant and post-liver transplant health states are markedly higher than the utility weights

used in Shepherd *et al*, (2006)[7]. The effect of these differences on the cost-effectiveness analysis of entecavir is explored in the ERG sensitivity analysis (section 4.4.1.4). The MS provides no justification for assuming the utility weight associated with the "Flare due to resistance" state as equal to the utility weight associated with decompensated cirrhosis. This may not be a reasonable assumption.

The adverse effects of pegylated interferon alpha 2a and the associated reduction in HRQoL were reflected in a utility decrement, which applied to the CHB state for the duration of therapy. This is consistent with the assumptions used in other published economic evaluations (Wong et al, 1995[35], Veestra et al, 2007[25]). Although this approach is reasonable, the reduction in utility weights does not correspond to the associated cost of treatment of adverse effects of pegylated interferon alpha 2a. In Shepherd *et al*, (2006) [7] an additional cost of physician visits and investigative tests associated with treatment of adverse events of pegylated interferon alpha 2a was included. Exclusion of these additional costs may potentially bias the cost-effectiveness estimate in favour of entecavir.

Overall the approach used in assigning utility weights to life years gained over the lifetime duration of the model seems reasonable. However, the difference between utility weights applied to the population in the compensated cirrhosis state, liver transplant and post-liver transplant health states in the MS model and the model reported in Shepherd *et al*, (2006)[7] creates a source of uncertainty. The difference in utility values between the MS models and the model in Shepherd *et al*, (2006)[7] is explained by the different methods of eliciting utilities.

Resource use

Two types of resources are used in the models: medications (initial therapy and salvage therapy whenever applicable) and the resources used in monitoring and treatment of patients in different health states. Unit costs for the standard doses of medications included in the economic evaluation were obtained from the most recent version of the British National Formulary (BNF) (issue 54, September 2007).

In nucleoside naïve HBeAg-positive and HBeAg-negative patients the initially prescribed dose of entecavir is 0.5 mg once daily. In lamivudine-refractory patients the recommended dose is 1 mg daily.

The prescribed comparator medication doses for nucleoside naïve HBeAg-positive and HBeAg-negative patients are:

- Telbivudine - 600 mg once daily;
- Lamivudine - 100 mg once daily;
- Pegylated interferon alpha 2a - 180 mg injection once weekly.

In patients who have failed prior lamivudine therapy the dose of comparator salvage therapy of lamivudine and adefovir is lamivudine 100 mg plus adefovir 10 mg once daily.

Table 27 presents the unit prices per pack and the annual costs of medication.

Table 27 Costs of the medication used in economic evaluation

Medication	Unit price per pack (£)	Annual cost in 2007 prices (£)
Entecavir 30-tablet pack 0.5 mg (1mg)	378.00	4,599*
Lamivudine 28-tablet pack 100 mg	78.09	1,018
Peg IFN 180-mg pre-filled syringe	132.06	6,339
Telbivudine 28-tablet pack 600 mg	290.33	3,785
Adefovir 30-tablet pack 10 mg	315.00	3,833

Peg IFN =pegylated interferon alpha 2a;
*the same price applies to the 30-tablet pack 1mg

Results of the calculation of the annual cost of each therapy based on the standard doses are presented in Table 6.10 of the MS and are correct.

Costs

Estimates of the costs of management of patients in different health states (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) are not presented in natural units with the corresponding unit costs. The MS stated on p.129 that, where possible, health state costs were taken from the model published by Shepherd *et al*. (2006)[7] and adjusted to 2007 price equivalents using the Gross Domestic Product (GDP)

deflator. It was assumed that service provision had not changed significantly in the last two years. Costs associated with individual health states were applied for the whole duration of the model.

Health state costs adopted for economic evaluation reported in Shepherd *et al*. (2006)[7] were estimated specifically for this assessment (NICE TA964). Table 28 presents health state costs used in the MS model.

Table 28 Health state costs used in economic evaluations

Health states	Annual costs in 2007 prices (£)	Source /Assumptions
CHB	565	Shepherd *et al* (2006)
Seroconversion/Response	281	Shepherd *et al* (2006)
HBsAg Seroconversion	32	Shepherd *et al* (2006)
Flare due to resistance	9,600	Assumed to be the same as decompensated cirrhosis
Resistance to treatment	565	Assumed to be the same as CHB
Active/compensated cirrhosis	1,198	Shepherd *et al* (2006)
Inactive cirrhosis	565	Assumed to be the same as CHB
Decompensated cirrhosis	9,600	Shepherd *et al* (2006)
Hepatocellular carcinoma	8,554	Shepherd *et al* (2006)
Liver transplant	38,723	Shepherd *et al* (2006)
Post-Liver transplant	1,457	Shepherd *et al* (2006)

The MS provides no justification for assuming the costs associated with the “Flare due to resistance” state as equal to the costs associated with decompensated cirrhosis. This may not be a reasonable assumption.

4.4.1.3 Consistency

Internal consistency

Random checking has been performed for some of the key equations in the model. The ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable and inputs changed on the ‘Inputs’ worksheet produce changes in the deterministic

results (shown in the 'Results' worksheet). These can be used to replicate the results presented in the MS and the univariate sensitivity analyses for the base case model, as reported in Tables 6.11 and 6.12 in the MS. The ERG conducted sensitivity analyses to see if the results go in the right direction and at around the expected magnitude, and were satisfied that the model appeared to be consistent in this regard.

The model is generally well presented and documented and is user friendly. The model includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on the 'Inputs' worksheet. The ERG view the model as a reasonable approach to modelling the cost effectiveness of entecavir, and from random checking the coding of the model appears to be accurate.

External consistency

The MS states that the external consistency of the model has been checked by consulting with clinical experts, comparing the model inputs with the previous CHB model developed by Shepherd *et al* (2006)[7] , and comparing the model results with those from previous models to check they were of a similar order. The MS claims that the results of the model are consistent with other published economic evaluations, although it does not indicate how closely the results from their model matched those of other models. Furthermore, they report that they conducted a systematic review of published economic evaluations of CHB treatment to inform assumptions within the model (see MS section 6.1 and Appendix 8.6). They mention that the model has also been reviewed by an independent statistician and modeller.

4.4.1.4 Assessment of Uncertainty

One-way sensitivity analyses

A series of one- way sensitivity analyses were carried on the base case model for all inputs in the model for the HBeAg positive and negative patients respectively. The parameters used in the one-way sensitivity analyses of entecavir versus lamivudine are shown in MS Tables 6.3, p113 and the results are shown in Table 6.14 and 6.15, p135-6 in the MS. The results shown are those parameters which have the most impact on the results. The inputs were varied around the confidence intervals for the transition probabilities, or by +/- 25% for the costs. The ranges

for treatment effectiveness varied according to the confidence interval values obtained from the MTC. However, the drug costs and the utility values were varied by only 5% and the ERG would consider varying these by more to show the uncertainty around these estimates, e.g. +/- 20%. The sensitivity analyses were presented for the entecavir versus lamivudine comparison only.

The results of the one-way sensitivity analyses versus pegylated interferon alpha 2a and telbivudine are presented in MS Appendix 8.8. The manufacturer has provided no comments on these analyses.

The models included a button 'run one way sensitivity analyses' which ran all the sensitivity analyses and ranked them in order of sensitivity of the parameters and showed these results in the 'TornadoResult' worksheet. This provided a slightly different ranking of the order of sensitivity of the parameters to that shown in Table 6.14 and 6.15.

ERG sensitivity analysis

The ERG updated the sensitivity analyses shown in the MS Table 6.14 and 6.15. The utilities and drug costs were varied by +/- 20% and this gave a slightly different ranking of the parameters from the MS as shown below in

Table 29 (HBeAg positive patients) and Table 30 (HBeAg negative patients). The model for HBeAg positive patients is most sensitive to changes in response and CHB utility rates and the transition probabilities from CHB to compensated cirrhosis and CHB to seroconversion.

The model for HBeAg negative patients is most sensitive to changes in the response rates and resistance utility, the transition probabilities between compensated cirrhosis and decompensated cirrhosis and between CHB treatment and compensated cirrhosis.

Table 29 Results of one-way sensitivity analyses for entecavir versus lamivudine as first line antiviral therapy in HBeAg positive nucleoside naive patients

		Low value		High value		
Parameters:	**Base Case**	**Value**	**ICER (£/QALY)**	**Value**	**ICER (£/QALY)**	**Range (£/QALY)**
Resistance Utility	0.88	0.70	5529	1.00	-168227	173756
CHB to CC. Baseline	0.04	0.004	48797	0.08	9541	39256
CHB Utility	0.88	0.70	-29084	1.00	7101	36185
CHB to SC, LMV, year 1	0.18	0.13	8831	0.24	28984	20152
CHB to SC, Baseline	0.09	0.06	29388	0.12	9647	19740
Discount rate, benefits	0.04	0.00	5657	0.06	24422	18765
CHB to SC, LMV, year 2	0.07	0.01	10878	0.16	23456	12578
CHB to SC, ENT, year 1	0.18	0.15	21868	0.22	9591	12276
CHB to SC, ENT, year 2	0.10	0.06	21220	0.16	9629	11591
Resist to SC, LMV, years 6+	0.09	0.06	10398	0.12	18989	8591
HBsAg- negative Utility	0.91	0.73	20047	1.00	12557	7489
Seroconversion Utility	0.91	0.73	18420	1.00	12911	5509
Discount rate, costs	0.04	0.00	12163	0.06	15123	2960
CC To DC Baseline	0.05	0.03	15956	0.07	13013	2943

CC = compensated cirrhosis; DC = decompensated cirrhosis; SC=Seroconversion (HBeAg); ENT=entecavir; LMV=lamivudine

Scenario Analysis

The MS provided additional scenario analyses to explore some the model assumptions. For the HBeAg positive model, entecavir is compared with the adefovir and lamivudine combination in a nucleoside naïve patient population and the model shows it is a dominant treatment. This was based on a non-statistical indirect comparison, and caution is therefore advised when interpreting these results

An analysis was also conducted assuming no disutility for patients receiving pegylated interferon alpha 2a treatment and the ICER increased from £8,403 to £11,899 per QALY. The MS also explored the scenario where patients received six months of consolidation therapy after HBeAg seroconversion. In this case the results were slightly less favourable than the base case but the conclusions were similar (MS Table 6.21).

Table 30 Results of one-way sensitivity analyses for entecavir versus lamivudine as first line antiviral therapy in HBeAg negative nucleoside naive patients, for lifetime treatment duration

		Low value		High value		
Parameters:	**Base Case**	**Value**	**ICER (£/QALY)**	**Value**	**ICER (£/QALY)**	**Range (£/QALY)**
Response Utility	0.91	0.73	37779	1.00	13226	24552
Discount rate, benefits	0.04	0.00	10813	0.06	23083	12270
CHB tx to CC. LMV, year 1	0.09	0.06	21504	0.12	14476	7028
Resist to CC. Active tx Baseline	0.09	0.06	20655	0.12	14808	5847
Resistance Utility	0.88	0.70	13939	1.00	19647	5708
Response to HCC	0.00	0.00	15358	0.01	21014	5656
CHBtx to CC. Entecavir	0.09	0.06	14594	0.12	20197	5603
CC Utility	0.87	0.70	14316	1.00	19417	5101
CC to DC	0.05	0.03	19750	0.07	14870	4880
Resist. Entecavir, year 4+	0.00	0.00	15349	0.01	19847	4498
CC active to HCC Baseline	0.03	0.01	19531	0.04	15232	4299
CHB to Response LMV, year 1	0.72	0.60	14900	0.82	19064	4164
Discount rate, costs	0.04	0.00	14301	0.06	17844	3543
Resist to Response salvage of lamivudine	0.60	0.49	15216	0.71	18436	3220

CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC=Hepatocellular carcinoma; LMV=lamivudine; tx=treatment

For the HBeAg-negative model, lifetime treatment duration was explored in a scenario analysis as shown in Table 6.22 in the MS and in Table 31 below. In this scenario, entecavir remained cost-effective, compared with lamivudine and pegylated interferon alpha 2a, with ICERs higher than the base-case scenario of five years of treatment. Entecavir also became dominant over telbivudine.

Table 31 Cost-effectiveness results for entecavir as first-line antiviral therapy in nucleoside naïve HBeAg-negative patients (lifetime treatment duration)

	Life years	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	18.34	16.42	72,923	9,351	82,274	
Lamivudine	17.63	15.58	55,574	12,586	68,160	16,850
Peg IFN	17.38	14.23	55,255	13,749	69,003	11,100
Telbivudine	17.99	16.00	81,503	11,186	92,689	Entecavir dominant

ERG scenario analysis

In the HBeAg positive model, patients with CHB were treated for two years with entecavir, lamivudine or telbivudine. The ERG's clinical advisor considered that patients would be treated for a much longer duration than two years. The ERG ran the model for longer treatment duration (Table 32). This showed that the ICER increased according to treatment duration, for example the ICER for 20 years of treatment duration was around £30,000 per QALY.

Table 32 Cost effectiveness results for entecavir versus lamivudine in HBeAg positive nucleoside naïve patients for different treatment durations

Treatment duration	Incremental QALYs	Incremental Costs	ICER (£)
2 years (Base case)	0.23	3261	14,329
5 years	0.24	5307	22,107
10 years	0.23	6170	27,120
20 years	0.22	6603	30,334

In the manufacturer's model, only pre-cirrhotic patients receive treatment (i.e. once the patients transit to the active cirrhosis state, the treatment is terminated). However, the ERG clinical expert reviewer felt that patients who progress to the compensated cirrhosis state do not cease treatment. The ERG ran the HBeAg negative model with patients with compensated cirrhosis receiving treatment for a lifetime duration, comparing entecavir with lamivudine. It was assumed that those with compensated cirrhosis receiving treatment would have a similar progression to decompensated cirrhosis, and that this transition probability would be 1.8% as used in Shepherd *et al* 2006[7] for lamivudine. In this scenario the ICER increased to £27,124 per QALY.

The MS model assumed that a certain proportion of patients receiving CHB treatment would develop flares followed by resistance to treatment. The ERG clinical expert advisor felt that this is a simplification of the actual progression of disease. The ERG also raised concerns about the uncertain direction of patients moving between flares and resistance (i.e. which comes first) and the cycle length of one year. The ERG ran the HBeAg negative model with the transition probability from CHB to "flares due to resistance" set to zero. The ICER of entecavir versus lamivudine increased slightly to £13,359 per QALY.

The MS assumed that all patients started in the CHB health state, however in practice a certain proportion of patients may first present at the stage of compensated cirrhosis. The ERG ran the HBeAg negative model with 90% of patients starting with CHB and 10% patients starting treatment with compensated cirrhosis. The ICER for entecavir vs lamivudine increased to £34,006 per QALY. When the proportion was further increased with 20% of patients starting treatment at the stage compensated cirrhosis (and 80% of patients starting with CHB) the ICER increased further to £42,608 per QALY. Treatment of patients who first present at the stage of compensated cirrhosis appears to be much less cost effective than treating patients who first present at the pre-cirrhosis state.

The ERG explored the assumptions of treatment durability in the HBeAg negative model. The MS assumed that after stopping treatment, 70% of individuals had a relapse from response to CHB. The ERG varied this between 50% and 90% for entecavir and lamivudine after treatment for five years and the ICER varied between £9,944 and £18,335 respectively.

As mentioned earlier in section 4.4.1.2, the ERG questioned the use of 7.2% for the treatment response rate in the second year with lamivudine in the HBeAg positive model, and suggests the value should be 14.4%. Using this value increased the ICER from £14,329 to £21,167 per QALY.

The manufacturer's models were run using the utility values suggested by Shepherd *et al*[7] (Table 4.6). In this case the ICER reduced from £14,329 to £10,386 and £16,850 to £11,781 in the HBeAg positive and negative models respectively. Most of the differences between the results were due to changes in the values for compensated cirrhosis.

Probabilistic Sensitivity Analysis

The MS presents a probabilistic sensitivity analysis (PSA) for the HBeAg positive and negative patients respectively (MS section 6.3.3.2). Results of the PSA for the HBeAg positive lamivudine-refractory patient population are presented in the Appendix 8.8 of the MS.

The PSA can be run from the 'Prob Outputs' worksheet by clicking on the 'Run PSA' button. It runs 10,000 iterations which takes about 20 minutes to run for the HBeAg positive model. The MS contains a scatterplot for entecavir vs telbivudine for the HBeAg positive model (Figure 6.4, p137 in MS), and cost effectiveness acceptability curves (Figures 6.5 and 6.6 in MS, p138,139) for each of the drugs for both disease models.

The parameter estimates used for the PSA were consistent with those used for the deterministic analysis. With the exception of results derived from the MTC, beta distributions are assigned to all transition probabilities and log-normal distributions to all relative risks. For results derived from the MTC, normal distributions are used to sample values for both log-odds and log-odds ratios, and these values are then used to generate the relevant transition probabilities. Drug costs are assumed to be known with certainty and thus have no associated distributions. Uncertainties surrounding health state costs are represented using log-normal distributions, with a range of +/-25% of the central estimate being used to generate 95% CIs. Uncertainties around the utility estimates are represented using beta distributions, with a range of +/-5% being used to generate 95% CIs. The distributions chosen appeared reasonable. The ERG considers that the range for utilities should be wider than 5%.

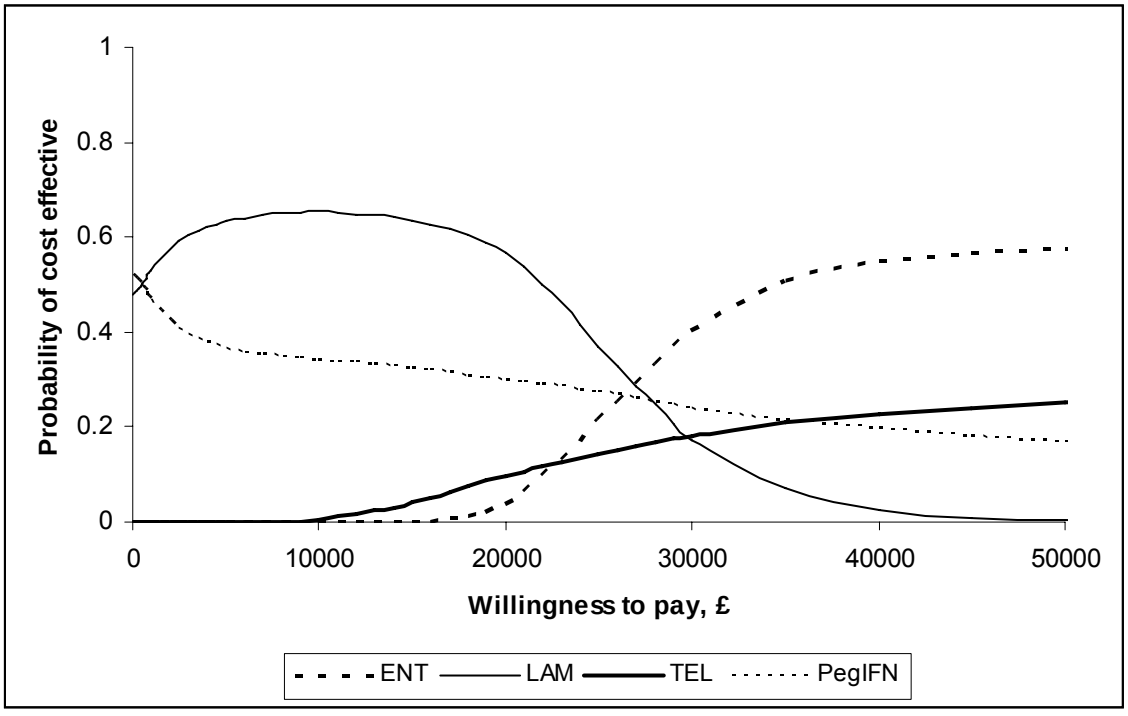
The results for the PSA in the MS show that entecavir has a probability of the ICER being below £20,000 of 57% versus lamivudine; 82% versus pegylated interferon alpha 2a; and 45% versus telbivudine in HBeAg positive patients (MS Table 6.16). For HBeAg negative patients the probabilities were 90%, 100% and 96% respectively (MS Table 6.18). The ERG ran the PSA in HBeAg positive lamivudine refractory patients. The results indicate that a probability of the ICER of entecavir versus combination treatment of lamivudine with adefovir being below £20,000 of 66%.

4.4.1.5 ERG probabilistic sensitivity analysis

The ERG conducted a probabilistic sensitivity analysis using wider uncertainty around the utilities (+/-10%) and drug costs (+/- 20%) than presented in the MS. As noted above, in the HBeAg positive model, patients with CHB were treated for two years with entecavir, lamivudine or telbivudine but, it was considered more appropriate for them to be treated for longer. The ERG attempted to run the HBeAg positive model for a longer duration but the results were inconsistent with those from the deterministic scenario analyses.

The ERG ran the HBeAg negative model for a lifetime treatment duration. The model was amended so that patients with compensated cirrhosis would also receive treatment, lasting until they develop decompensated cirrhosis, HCC or die. As can be seen from Figure 3, according to the manufacturer's model, the probability of entecavir being cost effective at a willingness to pay of £20,000 and £30,000 is 4% and 40% respectively.

Figure 3 - Cost effectiveness acceptability curve for entecavir, lamivudine, telbivudine and pegylated interferon for the HBeAg negative model



ENT= entecavir; LAM = lamivudine; TEL = telbivudine, PEG IFN = pegylated interferon alpha

4.4.2 Comment on validity of results presented with reference to methodology used

In general, the approach to the modelling is reasonable. However, the concerns are raised in relation to:

- The uncertain effect of the modelling assumption of patients with response transitioning exclusively to the inactive cirrhosis state;
- The appropriateness of including the "flare due to resistance state" given the uncertain direction of transitioning between flares and resistance (i.e. what comes first) and the cycle length of one year;
- The durations of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively, which do not correspond to clinical practice (where patients who do not achieve a response continue to receive treatment for life);
- The exclusion of patients who progress to the active cirrhosis state from receiving treatment for CHB;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease;
- The uncertainty in relation to the validity and reliability of some transition probabilities used in the model (e.g. probability of achieving a response in year two).
- Applicability of estimates of differential probabilities of transitioning to the active cirrhosis state in HBeAg positive patients who did not achieve seroconversion but nevertheless responded to treatment in terms of viral load suppression. The probability calculations rely on the relationship between the viral load and the risk of cirrhosis elicited from a single prospective, population-based cohort study of untreated Taiwanese individuals. It is uncertain whether the probability estimates obtained from the observational study and from the various studies of uncertain methodological quality (Lau *et al*, 2005[28], Han *et al*, 2007[31], Lai *et al*, 2005[27]) are (a) valid and (b) applicable to the UK population.
- The applicability of utility weights elicited from 100 uninfected UK residents to the entire population of CHB patients; also the unexplained discrepancy in utility values assigned to the patients in the compensated cirrhosis state, liver transplant and post-liver transplant health states in the MS model and the model reported in Shepherd *et al*, (2006)[7].

Given these concerns the ERG would suggest that the modelled economic evaluation might have produced an overestimate of the cost-effectiveness of entecavir in HBeAg positive and

HBeAg negative patients. The ERG agrees with the concerns raised by the manufacturer in relation to the cost effectiveness of entecavir in treatment of lamivudine-resistant patients.

4.4.3 Summary of uncertainties and issues

- The duration of treatment assumed in the models is poorly justified. The ERG clinical experts felt that for the majority of patients the treatment lasts longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models. The MS provided the lifetime treatment scenario for the HBeAg negative disease which the ERG clinical experts felt is the most appropriate model. However, there is an uncertainty associated with the paucity of clinical effectiveness data beyond the second year of treatment.
- Methods of deriving the year two estimates of response to treatment (footnotes to MS Tables 6.4 and 6.5) are not clear but appear to be based on the assumption of drop out rates being the same across all treatment groups. This assumption does not seem to be reasonable. The resulting estimates of response rates used in the model may bias the cost-effectiveness results in favour of entecavir.
- The model assumption about the clinical practice of excluding patients who progress to the active cirrhosis state from receiving further treatment for CHB is not supported by the ERG clinical expert. As demonstrated by the ERG scenario and PSA analysis, this assumption significantly biases the estimated ICER(s) in favour of entecavir.
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease is not supported by the ERG clinical expert. As demonstrated by the ERG scenario and PSA analysis, this assumption significantly biases the estimated ICER(s) in favour of entecavir.

5 Discussion

5.1 Summary of clinical effectiveness issues

- The evidence for the efficacy and safety of entecavir compared to lamivudine presented by the manufacturer comprises five published RCTs, which the ERG consider to be generally sound based on critical appraisal. The results of the individual trials show that entecavir is statistically superior across most outcomes. However, randomised data are only available for one year of treatment. Observational open-label follow-on studies are in progress which will report on the outcomes of treatment up to five years.

- There is a lack of head-to-head data for entecavir versus other comparators in both nucleoside naïve and lamivudine-refractory patients. The MTC model constructed by the manufacturer for nucleoside naïve patients permits both direct and indirect comparison of the drugs, but suffers from a number of weaknesses, particularly the lack of trials for some of the drugs in some of the patient sub-groups.
- None of the RCTs reported the impact of entecavir on health related quality of life. Consequently the manufacturer's submission lacks direct evidence on this important outcome.

5.2 Summary of cost effectiveness issues

The conceptual structure of the MS model appears reasonable and is generally in accordance with the decision problem and the NICE reference case. However, the ERG is primarily concerned about the following assumptions in the model that do not appear to correspond to clinical practice and are likely to have introduced a significant bias in the cost-effectiveness analysis in favour of entecavir:

- The duration of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively, which does not correspond to clinical practice where patients who do not achieve a response continue to receive treatment for life;
- The exclusion of patients who progress to the active cirrhosis state from receiving further treatment for CHB is not explained in the MS and does not reflect clinical practice;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease is not discussed in the MS and does not reflect clinical practice.

6 Appendices

Appendix 1: Manufacturer's response to clarification queries

Bristol-Myers Squibb response to clarification questions asked by the Evidence Review Group (ERG), received 24th December 2007

Responses to STA NICE/ERG Clarification letter 12th December 2007	
Approved name of medicinal product:	Entecavir
Brand name:	Baraclude
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	Toby Gosden
Position	Associate Director, Outcomes Research
Date:	21st December 2007

Section A: Clarifications of the effectiveness data

Literature searching

A1. It is stated that "no time limits were applied" for the clinical and cost effectiveness search strategies. Please can you specify the inception date of the databases (as this varies according to the host system used).

1) Clinical search strategy:

No date limits were applied to following databases - Inception dates of (where known) are shown:

- ***EMBASE using Dialog Datastar - 1974 to date ('date' = approximately the 21st September 2007)***
- ***MEDLINE using Ovid & Dialog Datastar - 1950 to date ('date' = approximately the 21st September 2007)***
- ***Cochrane Cochrane Systematic Reviews Database – 1800 to 2007 (default)***
- ***Cochrane Central Register of Controlled Trials – 1800 to 2007 (default)***
- ***DARE database – 1995 to present / HTA database – 1988 to present – searched jointly on Centre for Reviews & Dissemination website (www.crd.york.ac.uk)***

Inception dates could not be identified for the following databases (no date limits were specified in search):

- ***PreMedline using Dialog Datastar***
- ***Clinical trials clinicaltrials.gov website (www.clinicaltrials.gov)***
- ***Current Controlled Trials website (www.controlled-trials.com)***

2) Cost effectiveness search strategies:

No date limits were applied to following databases – Inception dates (where known) are shown:

- ***MEDLINE - 1950 to Sept 2007 / MEDLINE (R) In-Process (inception date not applicable) – searched jointly on pubmed (www.ukpmc.ac.uk)***
- ***EMBASE (1974 to present) /MEDLINE (1966 to present) - searched jointly on Embase website (www.embase.com)***
- ***DARE – 1995 to present; NHS EED – 1995 to present; HTA – 1988 to present – searched jointly on Centre for Reviews & Dissemination website (www.crd.york.ac.uk/)***
- ***Cochrane databases (see Cochrane Library - www.mrd.interscience.wiley.com/cochrane/) – default used of 1800 to 2007***

Inception dates could not be identified for the following databases (no date limits were specified in search):

- ***TRIP (www.tripdatabase.com)***

A2. Please could you specify which host system was used for the clinical effectiveness searches? It appears that the replication of the SHTAC search strategy (referred to as search #1 in Appendix 8.2, sub-section 8.2.4) was conducted using Ovid Medline. However the host system for searches #2 and #3 are not mentioned.

Host systems used for search strategy #2:

- ***Dialog Datastar (Embase)***
- ***Ovid & Dialog Datastar (Medline)***

Host systems used for search strategy #3:

- ***Ovid & Dialog Datastar (Medline)***
- ***Dialog Datastar (PreMedline; Embase)***
- ***Cochrane Library (www.mrd.interscience.wiley.com/cochrane/) for Cochrane Systematic Reviews Database & Cochrane Central Register of Controlled Trials***
- ***NHS CRD database website (www.crd.york.ac.uk) for DARE; Health Technology Assessment (HTA) database***
- ***Clinical trials.gov website (www.clinicaltrials.gov)***
- ***Current Controlled Trials website (www.controlled-trials.com)***

A3. Please could you provide the clinical effectiveness search strategies as tailored for each of the databases listed (e.g. Embase, Cochrane etc), together with the number of hits generated by each database. It would be useful to see how the strategy has been tailored for each database (and the results) so that it can be reproduced if necessary.

The results of the individual search strategies for each database were not saved by the agency commissioned to undertake the systematic review, therefore, these cannot be provided. The appendix at the end of this document does, however, provide the search strategies used for Embase, Medline (Dialog Datastar & Ovid) and the Cochrane Library databases. For the other databases (CRD databases, www.clinicaltrials.gov,

www.controlled-trials.com), each generic drug name combined with 'hepatitis B' was used in the search strategy.

A4. Search line 10 in the strategy #2 (Appendix 8.2) – at the end of the line is 'tnwas'. Please can you confirm whether this is recognised syntax or whether it is a typo (in earlier lines of the strategy 'tn' is used).

This is a typographical error. It should read: 10. (("polyethylene" and "glycol*") or "peg*"):ti,tt,ab,tn. To confirm, 'tn' was used in the search strategy rather than 'tnwas'.

A5. Search line 20 in the strategy #2 (Appendix 8.2) is recorded as '16 OR 17 OR lit OR 19'. We are unclear what 'lit' refers to and wonder whether it is a typo for '18'. If the latter please can you indicate what difference this makes to the search results.

'lit' was not used in the original search strategy. '18' was used instead. Hence this is a typographical error.

A6. Please can a list of the excluded studies be provided for each drug, with the reason for exclusion for each one (if possible).

A tabulation of the number of studies excluded by reason is provided in Appendix 8.3.2 of the submission. However, within the timeframe given to respond on these issues of clarification, it is not feasible to attribute the reason for exclusion to each study excluded.

Individual RCTs

A7. Tables 5.5, 5.6, and 5.7 list the proportion of patients attaining an HBV DNA of <300 copies/ML by PCR as well as the proportion attaining an HBV DNA of <0.7 ME/q/ML by branched DNA. These evaluations use different assays, but we are unclear as to how comparable they are in terms of a patient's viral load. Given that the proportions vary quite considerably between these two assays we would be grateful if you could clarify.

HBV DNA < 0.7 MEq/mL by bDNA is equivalent to 700,000 copies/mL.

A8. Table 5.1 (page 36) lists 12 RCTs of entecavir, yet the QUOROM flow chart (Fig 5.2.6, page 42) and Appendix 8.3.2 both list 10 papers. Please can you explain this discrepancy.

In addition to the 10 studies identified as relevant in the systematic review, two further studies were also identified from BMS internal records. The QUOROM flow chart (Fig 5.2.6, page 42) and Appendix 8.3.2 include only studies from the clinical systematic review. Table 5.1 includes the additional studies found from the search of BMS records.

A9. Table 5.5 (p.69) lists a complete virological response as 'HBV DNA and <0/7 MEq/ml by bDNA and ALT<1.25xULN'. However, on page 44 in the table a 'complete virological response' is defined as undetectable HBV DNA by bDNA assay and undetectable HBeAg. The figures presented in Table 5.5 correspond with those reported on page 1006 in the journal publication for this trial (Chang *et al*), which defines complete virological response as 'HBV DNA by bDNA assay and undetectable HBeAg'. Please can you clarify whether or not this is a typographical error.

This is a typographical error. In table 5.5 Complete virological response should be defined as undetectable HBV DNA by bDNA assay and undetectable HBeAg.

A10. Statistical significance not reported in Table 5.5 (p.69), 5.6 (p73) for the proportion of complete virological responders / partial responders / non-responders. We presume this is because these were not efficacy outcome measures per se, but governed whether or not patients proceeded to year 2 of treatment. Please could you clarify.

For the studies included in Tables 5.5 and 5.6 (studies 022 & 027), treatment comparisons (with statistical significance) at week 48 were conducted for complete virological responders, but not for partial responders or non-responders.

Throughout the submission publications were used as the primary data source for each study. Hence for study 022 (Table 5.5, page 69) statistical significance for complete virological responders at Week 48 was not reported in the table, as it was not available in the primary publication (Chang et al). Please find below the p value as reported in the CSR for this study (reference 57):

Endpoint	Entecavir 0.5mg N=354	Lamivudine 100mg N=355	Difference Entecavir-lamivudine (95% CI)	P-Value
Complete virological responders: HBV DNA <0.7 MEq/mL by bDNA and HBeAg negative, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Note: Commercial in confidence information is highlighted in above table

For Study 027 (Table 5.6, page 73) statistical significance for complete virological responders at Week 48 was reported in both the publication (Lai et al. (reference 58) and the CSR (reference 59) and is included in Table 5.6 (p73).

A11. Statistical significance is not reported for the year 2 cohort and 24 week post treatment follow-up for complete virological responders, as presented in Tables 5.5, 5.6, 5.7, and 5.8. Please can clarify why this was not presented, and supply the results if available.

According to the relevant clinical study reports, statistical comparisons for the year 2 cohort and 24 week post treatment follow-up for complete virological responders were not planned or undertaken for studies 022, 026, 027 and 023.

A12. Table 5.6 (p.73) states that patients were both HBeAg-ve and +ve in study 027, yet elsewhere this study is described as HBeAg-ve patients only. We presume this is a typographical error, please clarify.

To confirm that this is a typographical error, patients in study 027 were HBeAg-ve only.

A13. Table 5.9 the numbers for the patients in the entecavir and lamivudine groups should be 42 and 45 respectively as per Table 5.3.2, and not 141 and 145 respectively – we presume this is a typographical error carried over from table 5.8, please clarify

To confirm that this is a typographical error, the number of patients in the entecavir and lamivudine groups should be 42 and 45 respectively.

A14. Page 80 – we presume that in the table reporting secondary outcomes that the dose of entecavir should be 1.0mg not 0.5mg, as per table 5.3.2, please clarify

To confirm that this is a typographical error, the dose of entecavir should be 1.0mg not 0.5mg.

A15. Pages 75 and 76 – the total number of HBeAg positive patients in the study by Yao *et al* is reported as 255. However, for the percentages of patients responding on the various outcomes to make sense this needs to be 225, as is reported on page 74. Please can you clarify.

To confirm that this is a typographical error, the total number of HBeAg positive patients in the study by Yao et al is 225.

A16. Appendix 8.3, table at top of page 3. Under 'Final number for further review' there are 14 reports listed for entecavir – yet in the table on page 6 it says 18. Please clarify this discrepancy.

14 reports is an error. It should be 18 reports for both Appendix 8.3, table at top of page 3 and page 6.

Mixed treatment comparison

A17. Appendix 8.4 (mixed treatment comparison) – please could you clarify the role of adefovir in the analysis. Adefovir is not included as a comparator in the analyses for the naïve patient group, therefore is it included as a means of connecting entecavir with telbivudine? Also, the description of the model does not refer to any particular common comparator (although lamivudine appears to be common to most comparisons). Please can you clarify whether the analysis was designed around a common comparator.

In addition to using trial comparisons with lamivudine to connect entecavir with telbivudine, adefovir was used in the mixed treatment comparison to strengthen this connection. The analysis was based on a network of evidence and was not restricted to a common comparator for all interventions. For example, if there were four interventions A, B, C and D and information for A vs. B, B vs. C and C vs. D then it is possible to get information on A vs. D even though there is no common comparator between A and D. The analysis did use entecavir as the baseline against which all log odds were calculated but this does not mean that it is a common comparator.

A18. Appendix 8.4 (mixed treatment comparison) – Page 17 on the right hand side of the figure labelled 'HBeAg seroconversion' the study by Lai *et al* 2005a – doesn't appear to be connected to anything (the trial compares lamivudine with telbivudine), please can you clarify why.

Lai et al 2005a was a phase 2, dose escalation study comparing various doses of telbivudine to lamivudine given at the recommended dose. The study did not separate out results by dose for all endpoints and hence it was not possible to extract the relevant information. This meant that for some endpoints (e.g. HBeAg seroconversion) there was only information for one arm.

A19. Appendix 8.4 (mixed treatment comparison) it is stated that there were "110 studies identified as part of the review of clinical effectiveness". However, according to the figures presented in Appendix 8.3 we calculated that the number should be 109 (63 lamivudine; 15 pegylated interferon; 19 adefovir; 10 entecavir; 2 telbivudine). We presume this is a typographical; error, please clarify.

This is a typographical error. The 109 studies identified during the systematic review of clinical effectiveness were scanned for information relevant to the network meta-analysis.

A20. In Appendix 8.4 (mixed treatment comparison) on page 2 it reports that 19 published studies met the criteria for the MTC and a further 5 clinical study reports contained useful information. "Therefore 24 studies were included…". However, this figure may be incorrect. Three of the study reports appear to duplicate some of the 19 published studies:
a. Reference 4 – is the CSR for Study 022 which appears to relate to Reference 12 (Chang *et al* 2006)
b. Reference 6 is the CSR for Study 026 which appears to relate to Reference 25 (Sherman *et al* 2006)
c. Reference 7 is the CSR for Study 027 which appears to relate to Reference 18 (Lai *et al* 2006).
d. Therefore it would be more accurate to state that there were 24 reports describing a total of 21 studies. At present there appears to be double counting which erroneously inflates the number of actual studies in the MTC. Please can you clarify whether our calculations are correct.

It is correct that there were 24 reports describing a total of 21 studies. For each of the three studies listed above, the publications were used as the source for 1 year efficacy data, and the clinical study reports were used for all year 2 data.

A21. Were the studies included in the MTC assessed for their methodological quality?

Only randomised controlled trials were included in the MTC but a complete assessment of the methodological quality of each of these trials was not undertaken.

A22. Were any attempts made to estimate heterogeneity and if so what were the results?

There were insufficient data to allow a reliable estimate of a random effects variance to be obtained.

Section B: Economic Analysis

B1. Both models (i.e. for HBeAg+ve and HBeAg-ve sub-groups of patients) include a health state labelled "Flare d/t resistance" which is associated with an elevated risk of decompensated cirrhosis and liver transplant.

a. Please provide the source of clinical evidence (a publication and the page number with relevant estimates) for calculating the "Difference in flare rate between resistant and non-resistant patients".

Lok et al, Gastroenterology 2003;125: 1714-1722. Please see p. 1719, Table 4, row labelled 'ALT >10 x ULN'.

b. Please clarify the meaning of "Flare d/t resistance" health state, in particular, the statement "This is the *attributable* risk of severe flare due to resistance from Lok LMV safety summary" ('Inputs!' B153).

Flare due to (d/t) resistance is the annual incidence of severe flares (defined as ALT >10x ULN) for patients who develop resistance. In Table 4 of Lok et al 2003, the average rate of severe flare for patients with resistance across 5 years is approximately 2-3% per year.

c. Please clarify the clinical justifications of transition probabilities from the "Flare d/t resistance" health state to other states (Response, CHB Resist Salvage Tx, CHB no TX, etc.). In particular, please explain the clinical rationale of a transition probability from "Flare d/t resistance" to SC (seroconversion state) in the HBeAg+ve model. This non-zero probability does not correspond to Figure 6.3 (p.110) that has no transition between these 2 states depicted.

We did not identify any data on the probability of seroconversion ('Response') in patients who had experienced a severe flare due to resistance, and thus assumed they had a seroconversion rate the same as baseline, untreated patients.

The Flare health state is a tunnel state to reflect the clinical nature of a severe flare, which is a more acute event. Patients in the Flare state either develop complications (e.g. HCC, decompensation, liver transplant) or do not. Those patients that do not have a complication related to the flare, are likely to remain resistant and be on salvage therapy. In the model, this last group of patients move from the Flare state to the 'CHB Resist Salvage Tx' state.

The risks of complications (decompensation and liver transplant) from the Flare health state were estimated from Lok et al 2003 and Yuen et al 2003. Lok reported that roughly 5-20% of patients with ALT> 10xULN decompensated; Yuen et al in a study of 18 patients with LMV resistance and severe flares reported that 3 patients decompensated, 1 of whom required a liver transplantation and 1 of whom died.

Patients only move from the Flare state to the CHB no treatment (CHB no tx) state when treatment is stopped, which in the base case is 2 years for HBeAg+ve patients and 5 years for HBeAg-ve patients.

d. Please provide the rationale for a 9% transition probability from "Flare d/t resistance" to SC (seroconversion state), which is "Set Equal to CHB rate" ('Inputs!' H209).

Please see response above.

e. Also, please provide the clinical rationale for assigning transition probabilities from CHB to the "Flare d/t resistance" health state only to entecavir and interferon treatment in the HBeAg+ve model and only to entecavir and lamivudine treatment in the HBeAg-ve model.

All patients who experienced resistance should have a risk of severe flare (2% absolute risk). Interventions without resistance (at all, or in earlier years) will not have patients transitioning from CHB to 'Flare due to resistance'. Since there is no resistance in peginterferon use this is necessarily 0. Similarly, in the positive model when treatment is not being given the probability is necessarily 0. For all other occasions, for all drugs in both models, there is a (very small) probability derived.

Note that in the transition matrix sheets, only patients who are being treated (CHBtx) can experience flares; untreated patients (CHB) cannot.

B2. Both models include an "Inactive (non-replicating) cirrhosis" health state along with "Active (compensated) cirrhosis" state in both the HBeAg+ve and HBeAg-ve models. It appears from the HBeAg-ve model structure presented in the EXCEL spreadsheet that patients in "Response", "Response with resistance" and "Response to salvage Tx" health states can only enter the "Active cirrhosis" state via an "Inactive cirrhosis" state. The underlying clinical rationale for such structure of the model does not seem to be provided. The submission emphasises the importance of the [differential] risk of cirrhosis, however in the context of the clinical evidence (section 6.2.8) no distinction is made between inactive (non-replicating) cirrhosis and active (compensated) cirrhosis. Please provide clinical justification of the suggested disease progression pathway and explain the different roles of the "Inactive cirrhosis" and "Active cirrhosis" health states in the models.

In the HBeAg-ve model, patients who have achieved Response cannot progress directly to active cirrhosis. This is analogous to patients in the HBeAg+ve model who have achieved HBeAg seroconversion. These transitions were not allowed for consistency with the course of disease – patients with inactive disease are not likely to become cirrhotic with inflammatory response without first seroreverting or becoming HBV DNA positive.

The 'Inactive cirrhosis' health state was included to account for finer details of the disease that the clinicians we spoke to felt might be important to include in the model, although this state has relatively little impact on the results of the analyses. For example, the transition probability from response/seroconversion to the inactive cirrhosis state is 0.1%; increasing this estimate by even 10-fold has little effect. The estimate of progression from HBeAg-seroconversion to inactive cirrhosis was derived from Hsu et al, who described 189 patients that seroconverted and remained persistently HBeAg-negative with normal ALT over a 9-year follow-up. Of those, only 1 patient developed

cirrhosis during a median of 99 months of follow-up, which corresponded with an annualized incidence of cirrhosis of less than 0.1%.

B3. Was the clinical evidence used to obtain the estimate of a significantly lower risk of developing a decompensated cirrhosis (0.8%) (Fattovich *et al*, 2002, Table 6.3, p.113) observed in the population that is identical to the cohort of patients in the model (i.e. patients with "inactive cirrhosis")? Also, please provide a clinical rationale for assigning the value of transition probability from compensated cirrhosis to inactive cirrhosis as being equal to the probability of spontaneous response from the CHB state.

The patients in Fattovich et al. (2002) had compensated cirrhosis, which could be either active (HBV-DNA positive) or inactive (HBV-DNA negative), whereas in the model, the transition probability (inactive cirrhosis to DCC) refers to patients with inactive cirrhosis only. Rates of decompensation were not reported separately for active and inactive cirrhotic patients in Fattovich et al. but the study found that the risk of hepatic decompensation in patients with positive HBV-DNA (active cirrhosis) compared with patients with negative HBV-DNA (inactive cirrhosis) was approximately 4 fold higher (see Table 5, p. 2891). The annualised rate of decompensation of 3.1% in patients with both active and inactive cirrhosis (calculated from the percentage of HBsAg positive patients (20%) developing decompensation over a median of 77 months – see Table 2 p2889) was divided by 4 to obtain the 0.8% value for the inactive cirrhosis patients.

HBeAg-positive patients who have developed cirrhosis may still seroconvert and go into a non-replicative phase of disease (Liaw et al, Liver, 1989; 9(4):235-41). We did not have specific data on the probability of transitioning from active to inactive disease, and thus assumed this occurred at the same rate as that of baseline seroconversion (or probability of moving from CHB tx to Response). Changing the probability of transitioning from active to inactive cirrhosis has only a small impact on the incremental results – for instance, changing it from 9% to 0% changes the ICER in the entecavir vs. lamivudine comparison from £8,403 to £7,226 in the HBeAg positive model.

B4. What were the dose regimens and duration of therapy used in the scenario analysis of ENT monotherapy vs the combination of lamivudine and adefovir in treatment naïve patients? (p.140). Please provide the values of the estimates of clinical effectiveness of the ENT monotherapy vs LVD/ADV used in the scenario analysis.

For the comparison of ENT monotherapy vs LDV/ADV, the dose and duration of therapy for ENT were the same as that used in comparisons of ENT monotherapy with alternative monotherapies in HBeAg positive treatment naïve patients i.e. 0.5mg once daily for 2 years. The ADV/LDV combination uses the standard dosing regimens for lamivudine (100mg once daily) and adefovir (10mg once daily) combined.

In terms of clinical effectiveness, the seroconversion rates for years 1 and 2 for entecavir of 18.3% and 10.4% were taken from the network meta-analysis. The effectiveness of adefovir/lamivudine was taken from Marcellin et al. 2003, and rates of seroconversion of 12% in year 1 and 15.7% in year 2 were used. Rates of resistance for entecavir were taken

from the summary of product characteristics, and in the absence of specific resistance data for ADV/LVD in a naïve population, resistance was assumed to be the same as ADV monotherapy i.e. 0%.

Appendix

Embase search strategy

No.	Search term
1	hepatitis ADJ b OR hepatitis ADJ b ADJ chronic
2	hepatitis ADJ b ADJ virus OR hepatitis ADJ b ADJ antibodies
3	hbv OR hepatitis-b OR HBeag ADJ negative OR hbeag ADJ positive OR hbsag
4	1 OR 2 OR 3
5	pegylat$ ADJ interferon$ OR peg-ifn OR peginterferon$ OR pegasys OR pegintron OR viraferonpeg
6	interferon ADJ alpha ADJ 2a OR interfron ADJ alfa ADJ 2a OR interferon ADJ alpha ADJ 2b OR interferon ADJ alfa ADJ 2b OR alpha ADJ interferon OR intron OR viraferon OR roferon OR interferon-alpha OR interferon-alfa
7	interferon-alpha OR interferon-alfa
8	6 OR 7
9	polyethylene ADJ glycols
10	polyethylene AND glycol$ OR peg$
11	9 OR 10
12	8 AND 11
13	5 OR 12
14	13 AND 4
15	14 AND LG=EN
16	adefovir ADJ dipivoxil OR adefovir$ OR hepsera
17	telbivudine
18	lamivudine
19	entecavir
21	16 OR 17 OR 18 OR 19
22	21 AND 14
23	LG=EN
24	AT=ARTICLE OR AT=REVIEW OR AT=SHORT-SURVEY
25	22 AND 23 AND 24
26	22

Medline Search Strategy

#	Search History
1	(((hepatitis adj b) or hepatitis) adj b adj chronic).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2	(((hepatitis adj b adj virus) or hepatitis) adj b adj antibodies).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	(((((hbv or hepatitis-b or HBeag) adj negative) or hbeag) adj positive) or hbsag).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	1 or 2 or 3
5	((pegylat$ adj interferon$) or peg-ifn or peginterferon$ or pegasys or pegintron or viraferonpeg).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6	((((((((((interferon adj alpha adj 2a) or interferon) adj alfa adj 2a) or interferon) adj alpha adj 2b) or interferon) adj alfa adj 2b) or alpha) adj interfron) or intron or viraferon or roferon or interferon-alpha or interferon-alfa).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	(interferon-alpha or interferon-alfa).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8	6 or 7
9	(polyethylene adj glycols).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10	((polyethylene and glycol$) or peg$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11	9 or 10
12	8 and 11
13	5 or 12
14	13 and 4
15	limit 14 to english language
16	((adefovir adj dipivoxil) or adefovir$ or hepsera).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17	telbivudine.mp.
18	lamivudine.mp. or Lamivudine/
19	entecavir.mp.
20	16 or 17 or 18 or 19
21	20 or 15
22	limit 21 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or journal article or meta analysis or multicenter study or randomized controlled trial or "review")

Cochrane search strategy (for entecavir as an example)

1	“hepatitis b” AND entecavir
2	#1 and Cochrane Reviews

*these referred to five protocols (table below) – **not sure table below is necessary**

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Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) Clinical virologist

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
Available therapies include interferon, and nucelos(t)ide analogue reverse transcriptase inhibitors.
Is there significant geographical variation in current practice?
Not able to answer this from my own experience
Are there differences of opinion between professionals as to what current practice should be?
Management of chronic HBV infection is complex. The relative roles of IFN and NRTI-based therapies in managing an individual patient may not be clear.
What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
This is well summarised in the Final Scope document
Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Not aware of any evidence for this
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Management of chronic HBV infection is complex. With an increasing number of alternative effective drugs, this complexity will only increase. I believe treatment decisions should be made in specialist clinics with appropriate experience – either based in hepatology or infectious diseases.
There will be an increasing need to monitor the efficacy of anti-HBV drugs by viral load measurement, which is a fairly routine assay available in most diagnostic virology laboratories. Likewise, there will also be an increasing need for resistance testing, which is currently provided by very few specialist laboratories.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
I am unable to answer this question. I am not aware of variations.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
AASLD guidelines – Hepatology 2007; 45: 507-539
This contains an extensive review of all relevant published data.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I am aware of very little clinical experience of the use of telbivudine or entecavir in the management of chronic HBV infection in the UK. Thus, there is nothing to add other than data that have appeared in the literature.

As mentioned earlier, the development of these new forms of therapy should stimulate the need for easily available viral resistance testing services.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None to report

Implementation issues

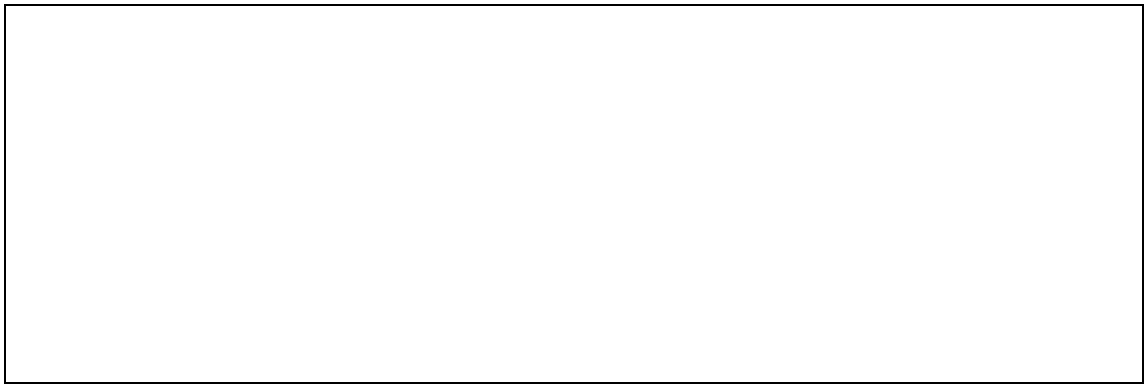
The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Allowance should be made for the increased costs of viral load monitoring and drug resistance testing as more patients with chronic HBV ifneciton are treated with nucleos(t)ide analogues.



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Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Physicians

Response coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Entecavir is a recently licensed oral antiviral agent used in the management of patients with chronic hepatitis B viral (HBV) infection. The drug is licensed for both HBeAg positive and HBeAg negative disease. At present there is relatively limited information on this drug and its place in the long-term management of patients with chronic HBV infection is still unclear. However, it is known that entecavir is a very potent antiviral agent and causes a very rapid decline in serum levels of HBV DNA. The drug is effective in the vast majority of treated patients and a very large proportion have undetectable circulating HBV DNA within six months of starting therapy.

Viral resistance is a very significant problem with current oral antiviral agents. Viral resistance is associated with disease progression and requires either a change in therapy or the addition of new drugs to combat resistance. At present the number of agents available for the management of chronic HBV is relatively low and there are fears that some patients may develop multi-resistant viral strains that are, effectively, untreatable. Drugs that reduce the development of viral resistance are required to prevent an accumulation of multi-drug resistant viral strains. Entecavir has a very high barrier to the development of resistance – clinical trials run by the manufacturers have shown that resistance is very uncommon, although the rates of resistance in clinical practice are not yet known. Based on available data it is probable that resistance in clinical practice will be rare. Entecavir is active against 'wild type HBV and viral strains that are resistant to other antiviral agents, such as lamivudine and adefovir and thus may be useful in both preventing and managing viral resistance.

As a potent antiviral agent with a low rate of resistance we believe that entecavir may be valuable in a wide range of clinical scenarios. Entecavir may be useful in the management of patients where a rapid reduction in viral load is desirable – for example in patients with high level viraemia who are being considered for transplantation or in patients with severe, acute hepatitis. In patients with HBeAg positive HBV entecavir has moderate seroconversion rates and suppresses viral replication in the majority of patients without a high risk of drug resistance. For patients with HBeAg positive HBV who prefer an oral drug, rather than an injectable drug such as interferon, entecavir is thus an attractive therapeutic option. In patients with HBeAg negative HBV infection entecavir is a potent drug that may permit long term control of viral replication with a single agent. The low rates of drug resistance may be very advantageous in this setting. Entecavir's activity against resistant strains of HBV is of very considerable advantage for patients who have become resistant to other antiviral drugs.

A number of drugs are currently available for the management of chronic HBV. These include pegylated interferon, lamivudine, adefovir and telbivudine. The optimal management strategy that maximises the long term benefits of these agents is still not clear and long term follow up studies will be required to define the ideal management approach. In studies extending up to two years entecavir has been shown to be one of the most potent anti-viral agents currently available and the very low rates of resistance seen in the clinical trials indicate that entecavir may be a very useful therapeutic agent. Entecavir is recommended as first line therapy for chronic HBV infection in many developed countries and we believe that UK physicians should have the option of using this drug as a first line agent for the management of patients with chronic hepatitis B.

BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD

ENTECAVIR (BARACLUDE®) FOR THE TREATMENT OF CHRONIC HEPATITIS B

SINGLE TECHNOLOGY APPRAISAL SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH & CLINICAL EXCELLENCE

NOVEMBER 2007

Confidential information is underlined and highlighted, e.g. [redacted].

Contents

List of abbreviations

ADV	adefovir dipivoxi
AE	adverse events
ALT	alanine aminotransferase
CHB	chronic hepatitis B
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
CT	clinical trial
EMEA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
ETV	Entecavir
FAD	Final Appraisal Determination
FDA	Food and Drug Administration
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B s antigen
HBV	hepatitis B virus
IC50	50% inhibitory concentration
IFN	Interferon
ITT	intention to treat
IU	International Unit
IV	Intravenous
LdT	Telbivudine
LLOD	lower level of detection
LOCF	last observation carried forward
LTE	long-term extension
LVD	lamivudine
LVDr	lamivudine-resistant
NA	nucleo(s/t)ide analogue
NDC	National Drug Code
NICE	National Institute for Health and Clinical Excellence
PCR	Polymerase Chain Reaction
pegIFN-α	pegylated interferon alpha
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled clinical trial
SAE	severe adverse events
SD	standard deviation
SE	standard error
SHTAC	Southampton Health Technology Assessment Centre
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	single technology appraisal
TAR	technology assessment review
ULN	upper limit of normal

Section A

1 Description of the technology under assessment

1.1 The technology

Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name	Baraclude®
Approved name	Entecavir
Proposed therapeutic class	Nucleoside and nucleotide reverse transcriptase inhibitors

1.2 UK marketing authorisation

Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates.

Entecavir has a UK marketing authorisation for the indications detailed in this submission. Marketing authorisation was granted on 26th June 2006.

1.3 Indication(s) in the UK

Entecavir is indicated for the treatment of chronic hepatitis B (CHB) infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This indication is based on clinical trial data in patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative hepatitis B virus (HBV) infection, nucleo(s/t)ide analogue (NA)-naïve patients and patients with lamivudine-refractory hepatitis B[1].

1.4 Current use in the NHS

To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Entecavir is available for use in the UK for the treatment of CHB in patients with HBeAg-positive and HBeAg-negative HBV infection. Patients may be treatment-naïve or have failed prior HBV therapy[1]. There are no adult patients currently being treated with entecavir in the UK in manufacturer-sponsored clinical studies. Paediatric patients are about to be recruited in the UK for AI463-028, a manufacturer-sponsored study evaluating the pharmacokinetics, safety, tolerability and efficacy of entecavir in paediatric subjects with CHB infection who are HBeAg-positive. Treatment of the first patient in the UK is expected to be scheduled for the 14th of December 2007.

1.5 Regulatory approval outside the UK

Does the technology have regulatory approval outside the UK? If so, please provide details.
Entecavir has marketing authorisation approval in over 50 countries around the world (see below). This includes countries in the European Union, non- EU European countries, the Americas, Asia, Africa, Australia and the Middle East.

Argentina	India	Qatar
Australia	Indonesia	Russia
Brazil	Japan	Saudi Arabia
Burkina Faso	Jordan	Singapore
Canada	Kenya	Switzerland
Chile	Korea	Taiwan
China	Kuwait	Thailand
Colombia	Macau	Trinidad and Tobago
Democratic Republic of Congo	Malaysia	Turkey
Dominican Republic	Mexico	Uganda
Ecuador	Namibia	United Arabic Emirates
Egypt	New Zealand	United States
El Salvador	Norway	Venezuela
European Union	Pakistan	Vietnam
Guatemala	Peru	Zimbabwe
Hong Kong	Philippines	
Iceland	Puerto Rico	

1.6 Other UK health technology assessments

Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?
Entecavir has been assessed by the Scottish Medicines Consortium which issued the following advice[2]:

"Entecavir (Baraclude®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and or fibrosis. Clinical studies have shown that entecavir is more effective than lamivudine in NA-naïve HBeAg-positive and -negative patients and in lamivudine-refractory patients."

1.7 Formulations

For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?
Entecavir is supplied as 0.5-mg and 1.0-mg film-coated tablets in cartons, each containing 30 blister-packed tablets. An oral solution is also available for patients with renal impairment who require reduced daily dosing[1].

1.8 Proposed course of treatment

What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.
Entecavir is taken orally once daily (qd). For NA-naïve patients, the recommended dose is 0.5 mg qd, with or without food. For lamivudine-refractory patients (i.e. those with lamivudine-resistant mutations or evidence of viraemia while on lamivudine): the recommended dose is 1 mg qd, which must be taken on an empty stomach (>2 hours before or >2 hours after a meal). Dose reductions are required for renally impaired patients.

The optimal duration of treatment is unknown. The summary of product characteristics (Appendix 8.1)[1] states that treatment discontinuation may be considered as follows:

- In HBeAg-positive patients, treatment should be administered at least until HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples taken at least 3–6 months apart), or until HBs seroconversion or there is evidence of loss of efficacy.
- In HBeAg-negative patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for >2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

1.9 Acquisition cost

What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.
The acquisition cost of entecavir is[3]:

- Film-coated tablets, entecavir (as monohydrate)
  - 500 μg (white), net price 30-tablet pack = £378.00
  - 1 mg (pink), net price 30-tablet pack = £378.00
- Oral solution, entecavir (as monohydrate)
  - 50 μg/mL, net price 210-mL pack (orange flavoured) = £441.00

1.10 What is the setting for the use of the technology?

Entecavir is used in UK clinical practice for treatment of CHB in line with its European Agency for the Evaluation of Medicinal Products (EMEA) marketing authorisation.

Therapy should be initiated by a physician experienced in the management of CHB infection. Entecavir is an oral regimen and is self-administered by patients at home.

1.11 Other aspects of treatment

For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be

administered at the same time as the intervention as part of a course of treatment?
Therapy should be initiated by a physician experienced in the management of CHB infection. No additional tests or investigations will be required beyond those already employed in routine clinical practice. No other therapies need to be routinely administered at the same time as entecavir as part of a course of treatment.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	**Decision problem(s) addressed in the submission**
Intervention(s)	Entecavir alone or in combination with other therapies	Entecavir alone
Population(s)	Adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation)	Adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation)
Current standard comparators	• interferon α-2a (IFNα-2a) • IFNα-2b • pegylated IFNα-2a (pegIFNα-2a) • lamivudine • adefovir dipivoxil • telbivudine	• IFNα-2a • IFNα-2b • pegIFNα-2a • lamivudine • adefovir dipivoxil • telbivudine

Outcomes	Outcomes to be considered include: • HBeAg/HBsAg seroconversion rate • virological response (HBV DNA) • histological improvement (inflammation and fibrosis) • biochemical response (e.g. ALT levels) • development of viral resistance • time to treatment failure • survival • health-related quality of life (HR-QoL) • adverse effects of treatment	Outcomes to be considered include: • HBeAg/HBsAg seroconversion rate • virological response (HBV DNA) • histological improvement (inflammation and fibrosis) • biochemical response (e.g. ALT levels) • development of viral resistance • time to treatment failure • survival • HR-QoL • adverse effects of treatment
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY).	The cost-effectiveness of treatment with entecavir will be expressed in terms of incremental cost per QALY.
	The time horizon for the economic evaluation should reflect the chronic nature of hepatitis B. Consideration should be given to alternative treatment continuation rules as appropriate.	The time horizon for the economic evaluation will reflect the chronic nature of hepatitis B; analyses will be presented for a lifetime horizon. The analyses will be conducted in accordance with the NICE reference case for economic evaluation.
	Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.	Costs will be considered from a NHS and PSS perspective.

Other considerations	If evidence allows, the appraisal will seek to identify subgroups of individuals for whom the technology is particularly clinically and cost-effective. Subgroups may include people with HBeAg-positive, HBeAg-negative and treatment-resistant disease types. In line with NICE technology appraisal 96[4], this STA will not specifically consider people with CHB known to be co-infected with hepatitis C, hepatitis D or HIV. If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy.	Based on clinical evidence, this submission separately analyzes the HBeAg positive, negative and lamivudine resistant disease types. In line with NICE technology appraisal 96[4], this submission will not specifically consider people with CHB known to be co-infected with hepatitis C, hepatitis D or HIV. If the evidence allows, the submission will consider sequential use of antiviral drugs and combination therapy.
	Guidance will be issued in accordance with the marketing authorisation.	For this appraisal, the intervention is in accordance with the marketing authorisation.

Section B

3 Executive summary

3.1 Context

Hepatitis B is an infectious disease caused by the Hepatitis B Virus (HBV). Chronic Hepatitis B (CHB) is defined as a chronic necroinflammatory disease of the liver with persistence of HBsAg for >6 months. Infection can be categorised into two groups: 'HBe-positive virus' and 'HBe-negative virus' infection. In the UK, CHB affects approximately 180,000 people (0.3% of the population) with an estimated 7,700 new cases of CHB each year, 96% of which are immigrants to the UK. Individuals with CHB are at an increased risk of developing liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), each with significant QoL and health service cost implications. Some CHB patients will also require high-cost liver transplantation.

There are two main classes of drug used in the treatment of CHB: Interferons (IFNs) and Nucleoside analogues (NAs). Of the IFNs, pegIFN is the most commonly used and is recommended by NICE as an option for first-line therapy. However, due to its limited efficacy and safety profile, pegIFN is considered suitable for short-term but not long-term treatment of CHB, in a limited patient population. NAs act directly to inhibit viral replication. In addition to Baraclude® (entecavir, ETV), there are three other antiviral agents licensed for the treatment of CHB in the UK: lamivudine, adefovir and telbivudine. Long-term treatment with NAs can result in an increase in the selection and emergence of resistant HBV strains, which can limit future treatment options and increase disease progression. The ultimate goals of therapy are to decrease the incidence of cirrhosis, end-stage liver disease, HCC and liver-related mortality; however, these long-term goals are difficult to evaluate in clinical trials. Instead, surrogate endpoints such as decrease in serum HBV DNA, HBeAg seroconversion (in patients who were initially HBeAg-positive), HBsAg seroconversion, normalisation of biochemical markers (serum ALT levels) and improvement in liver histology are used to assess treatment efficacy. Increasing evidence is emerging to establish viral load as an important predictor of CHB disease progression. Therefore a recognised aim of treatment is to achieve sustained suppression of HBV replication, with the avoidance of resistance and remission of liver disease. Consequently, the preferred NA should combine superior efficacy with low resistance rates.

Entecavir is a HBV-specific guanosine NA that inhibits three phases of viral replication. It is approved for the treatment of chronic HBV infection in the UK and was granted a marketing authorisation in the European Union on 26th June 2006. Entecavir is indicated for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated ALT levels and histological evidence of active inflammation and/or fibrosis. Entecavir is supplied as either 0.5-mg or 1.0-mg film-coated tablets in 30-tablet blister-packed cartons. In addition, an oral solution is available for patients with renal impairment who require reduced daily dosing. For patients who have not received NA therapy previously (NA-naïve), the recommended dose is 0.5 mg once daily, with or without food, whereas 1 mg once daily is recommended in patients who have failed lamivudine therapy (lamivudine-refractory patients). The optimal duration of treatment is unknown but according to the SmPC treatment should be continued in HBeAg-positive patients until HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3–6 months apart) or until

HBs seroconversion or loss of efficacy. In HBeAg-negative patients, treatment should be administered until HBs seroconversion or evidence of loss of efficacy.

In this submission, the efficacy, safety and cost-effectiveness of entecavir are assessed in NA/treatment–naïve and lamivudine-refractory CHB patients. Separate analyses are performed for either HBeAg positive or HBeAg negative patients. In NA-naïve patients comparisons are made with two NAs (lamivudine and telbivudine) and for treatment-naïve patients, comparisons are made with the most commonly used IFN (pegIFN). Lamivudine is the most appropriate anti-viral comparator because it is the most commonly used therapy in the UK for NA-naïve patients. PegIFN is included as a comparator because it is recommended by NICE and telbivudine is included because it is currently being appraised by NICE. For lamivudine-refractory patients, adefovir plus lamivudine (ADV/LVD) combination therapy is the main comparator for entecavir because the use of add-on adefovir is recommended by NICE and it is the most commonly used treatment for this patient group in the UK.

3.2 Entecavir clinical effectiveness

For NA-naïve patients, entecavir should be the preferred antiviral therapy as it is more clinically effective in viral suppression with the lowest resistance rates.

In NA-naïve HBeAg-positive patients, entecavir is more clinically effective than other available first-line CHB therapies in viral suppression and is associated with the lowest resistance rates.

In NA-naïve HBeAg-negative patients, entecavir is more clinically effective than lamivudine and pegIFN and equivalent to telbivudine in viral suppression, and is associated with the lowest resistance rates among antiviral therapies.

In lamivudine-refractory patients, entecavir is a more clinically effective option compared with continuing lamivudine therapy in viral suppression.

3.2.1 Comparison with lamivudine in NA naïve CHB patients

The clinical evidence supporting this comparison is derived from head to head randomised trials of entecavir compared with lamivudine. One trial compared entecavir with lamivudine in HBeAg-positive patients only (022); another included only HBeAg-negative patients (027) and another included both (023) (see Section 5.4). In HBeAg-positive NA-naïve patients entecavir had statistically significant superior histological improvement (primary endpoint) after 48 weeks of treatment compared with lamivudine; 72% vs. 62% p=0.009 (study 022). At week 48, the percentage of patients with HBV DNA <300 copies/ml (measured by Polymerase Chain Reaction (PCR)) was also significantly greater: 67% vs. 36%, p<0.001. There was no significant difference in HBeAg seroconversion rates.

In HBeAg-negative NA-naïve patients the results also show that entecavir had statistically significant superior histological improvement (primary endpoint) after 48 weeks of treatment compared with lamivudine: 70% vs. 61%, p=0.01 (study 027). At week 48 the percentage of patients with HBV DNA <300 copies/ml by PCR was also significantly greater (90% vs. 72%, p<0.001). A network meta-analysis of data in HBeAg-positive and -negative patients confirm the findings of the head-to-head randomised controlled trials (RCTs), showing that the relative probability of viral load reduction after 48 weeks of treatment was significantly higher for entecavir than lamivudine.

Entecavir resistance data from six entecavir trials show that the cumulative probability of entecavir genotypic resistance was 1.2% in patients treated for up to 4 years (see Section 5.8.2). A comparison of genotypic resistance rates across all NAs (see Section 5.6.6) shows that entecavir is associated with much lower cumulative genotypic resistance rates compared with lamivudine (0.5% vs. 46% at year 2 and 1.2% vs. 71% at year 4). Entecavir resistance is rare in NA-naïve patients due to a rapid and sustained suppression of serum HBV DNA to undetectable levels and a high genetic barrier to resistance.

3.2.2 Comparison with pegIFN in NA-naïve CHB patients

The clinical evidence supporting this comparison was obtained by an indirect comparison (network meta-analysis) as no direct RCT comparator data are available (see Section 5.6). The network meta-analysis was performed for treatment-naïve HBeAg-positive and HBeAg-negative CHB patients separately, and on virological response, biochemical response and seroconversion. In HBeAg-positive patients, entecavir results in a significantly higher average predicted probability of viral suppression compared with pegIFN (Year 1: 68.8% [95% CI: 65.1–72.4] vs. 21.8% [14.5–30.5]). Entecavir was also superior to pegIFN in ALT normalisation (average predicted probabilities at year 1: 76.3% [72.9–79.6] vs. 43.9% [32.6–55.7]). HBeAg seroconversion rates were comparable, the mean predicted probabilities being 18.3% (15.4–21.4) vs. 24.5% (15.9–35.3) at year 1. In HBeAg-negative patients, entecavir was superior to pegIFN in viral suppression (mean predicted probabilities: 90.5% [87.3–93.3] vs. 61% [43.8–76.2] at year 1), and ALT normalisation (79.3% [75.0–83.4] vs. 36.2% [23.0–51.0] at year 1).

3.2.3 Comparison with telbivudine in NA-naïve CHB patients

The clinical evidence supporting this comparison was obtained by indirect comparison (network meta-analysis) as no direct RCT comparator data are available(see Section 5.6). The network meta-analysis was performed for treatment-naïve HBeAg-positive/-negative CHB patients on histological improvement, virological/biochemical responses and seroconversion (HBeAg-positive only). In HBeAg-positive patients, entecavir has a significantly higher average predicted probablity of achieving undetectable HBV DNA (Year 1: 68.8% [65.1-72.4]) vs. 55.7% [46.1-65.0] and is equivalent in terms of the other outcomes. In HbeAg-negative patients, entecavir is equivalent to telbivudine on all endpoints, except ALT normalisation where entecavir is superior (Year 1: 79.3% [75.0-83.4] vs. 64.8% [50.0-774]). A comparison of genotypic resistance rates across all NAs (see Section 5.6.6) shows that entecavir is associated with lower genotypic resistance rates compared with telbivudine (0.5% vs. 22% at year 2 in HBeAg-positive patients).

3.2.4 Comparison with lamivudine in lamivudine-refractory patients

Two head-to-head trials assessed entecavir versus lamivudine in lamivudine-refractory CHB patients (026 and 014) as described in Section 5.4. Entecavir had statistically significant superior histological improvement (primary endpoint) after 48 weeks of treatment compared with lamivudine: 55% vs. 28%, $p<0.0001$ (026). At week 48, the percentage of patients with HBV DNA <300 copies/ml (measured by Polymerase Chain Reaction (PCR)) was also significantly greater in the entecavir group: 19% vs. 1%, $p<0.0001$ (026). In lamivudine-refractory patients, the cumulative probability of virological breakthrough due to entecavir increased from 1% after 1

year to 41% after 4 years of therapy (see Section 5.8.2). No comparison could be made with other NAs due to lack of data.

3.2.5 Comparison with adefovir/lamivudine in lamivudine-refractory CHB patients

No direct RCT data is available to compare entecavir with adefovir/lamivudine in a CHB lamivudine-resistant patient population who are HBeAg-positive. A network meta-analysis could not be conducted due to paucity of data in the lamivudine-refractory HBeAg-positive population. An indirect comparison of available studies in HBeAg-positive patients shows that entecavir and lamivudine/adefovir are similar in rates of seroconversion and viral load reduction, however these results must be treated with caution as the analylsis does not adjust for any differences in methodology and patient characteristics.

3.3 Entecavir safety

An assessment of entecavir safety is based on summary information from the summary of product charateristics and head-to-head trial data where available (see Section 5.7). Data on adverse reactions in the SmPC is based on four RCTs in which 1,720 patients with CHB infection received treatment with entecavir 0.5 mg/day (n=679), entecavir 1 mg/day (n=183) or lamivudine (n=858) for up to 107 weeks (see Section 5.7.2). The safety profiles of entecavir and lamivudine, including laboratory test abnormalities, were comparable in these studies. The most common adverse reactions of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%).

3.4 Entecavir resistance

Resistance to entecavir in both NA-naïve and lamivudine-refractory patient populations were measured over 4 years in six trials (see Section 5.8.2). In NA-naïve patients treated with entecavir for up to 4 years there was a cumulative probability of virological breakthrough due to entecavir genotypic resistance (ETVr) of less than 1.2%.

Rates of genotypic resistance in NA-naïve patients for a number of antiviral therapies could be indirectly compared (see Section 5.6.6). At 2 years of treatment, entecavir has the lowest rates of genotypic resistance across both HBeAg positive and negative patients compared with lamivudine and telbivudine (0.5% vs. 46% and 9-22%, respectively). However, this analysis is not adjusted for differences between the trials compared in patient populations and methodology.

In lamivudine-refractory patients, the genetic barrier to resistance is lower, and the cumulative probability of incurring a virological breakthrough with ETVr increased from 1% after 1 year to to 11%, 27% and 41% after years 2, 3 and 4 (see Section 5.8.2).

3.5 Entecavir cost-effectiveness

Entecavir is a cost-effective first-line antiviral treatment for NA-naïve CHB patients compared with other first-line therapies in both HBeAg positive and negative patients. Cost-effectiveness analyses were undertaken comparing entecavir with lamivudine, pegIFN, and telbivudine in NA-naïve patients, and with

lamivudine plus adefovir in lamivudine-refractory patients. Separate Markov state transition models were developed for HBeAg-positive and HBeAg-negative disease groups. A 1-year cycle length was used for both models. Both models were originally developed in the USA and informed by a systematic search of the literature and clinical opinion, but were adapted for use in the UK so that the treatment pathway and all input parameters reflected current UK clinical practice. Both models have a similar structure to a model recently developed by the Southampton Health Technology Assessment Centre (SHTAC) for a recent NICE technology appraisal (TA96). Costs were taken from UK sources and publications identified in the systematic review, and utilities were determined from a UK study. The analyses were conducted in accordance with the NICE reference case for economic evaluation. The perspective is restricted to the UK NHS and PSS and the cost-base year is 2006.

The results of the cost-effectiveness analysis suggest that entecavir is a cost effective first-line antiviral therapy in HBeAg-positive and -negative patients with a cost per QALY versus lamivudine of £14,329 and £13,208, respectively. In the analysis against pegIFN, entecavir demonstrated cost-effectiveness with a cost per QALY of £8,403 and £7,511 as first-line CHB therapy in HBeAg-positive and HBeAg-negative patients respectively.

In terms of cost-effectiveness in HBeAg-positive patients, telbivudine and entecavir have similar efficacy with small difference in costs (telbivudine showing slightly lower cost of £187 versus entecavir over a lifetime horizon). The probabilistic sensitivity analysis demonstrates that entecavir and telbivudine are comparable in this patient population. In HBeAg-negative patients, entecavir was cost-effective compared with telbivudine with a cost per QALY of £6,907.

The analysis in the lamivudine-refractory HBeAg-positive patients that compared entecavir with the adefovir/lamivudine combination showed that entecavir was the dominant strategy. Entecavir remained a cost effective therapy in all scenario analyses, with incremental cost per QALYs below £30,000. This analysis should, however, be treated with caution due to paucity of data in the HBeAg-positive lamivudine-refractory population.

The results were tested in one-way, probabilistic sensitivity analyses and scenario analyses and were robust to variations in key parameters. The results of the model are also consistent with those of other published economic evaluations in CHB.

3.6 Budget impact

The estimated budget impact of entecavir in England and Wales was assessed for a 1-year period only by comparing total drug costs pre- and post-positive NICE guidance for entecavir. Pre-NICE guidance, entecavir was assumed to have a 0% market share whereas in the post-guidance period the market share was estimated to be approximately 8% of all treated CHB patients. Overall, 372 patients are estimated to be treated with entecavir in England and Wales with a net annual budget impact of £1.3 million.

3.7 Conclusion

There is a clear unmet need for an effective therapy for CHB patients due to the limited efficacy and poor resistance profile of existing therapies. For NA-naïve CHB patients, entecavir should be the preferred anti-viral therapy as it is more clinically effective in viral suppression with the lowest resistance rates and is a cost effective therapy. In NA-naïve HBeAg positive patients, entecavir is more clinically effective

than other available first-line CHB therapies in viral suppression, is associated with the lowest resistance rates and is a cost-effective use of NHS resources. In NA-naïve HBeAg negative patients, entecavir is more clinically effective than lamivudine and peginterferon and equivalent to telbivudine in viral suppression, and is associated with the lowest resistance rates among anti-viral therapies. Entecavir is a cost-effective first-line antiviral treatment for NA-naive CHB patients compared with other first-line therapies in both HBeAg-positive and -negative patients.

For lamivudine-refractory patients, entecavir is more clinically effective than continuing with lamivudine alone, and is cost-effective compared with adefovir/lamivudine combination therapy. Therefore entecavir should also be considered a treatment option for patients who develop resistance to first-line lamivudine.

4 Context

4.1 Overview of chronic hepatitis B

4.1.1 Etiology/epidemiology

Hepatitis B is an infectious disease caused by infection with HBV. CHB is defined as a chronic necroinflammatory disease of the liver with persistence of HBsAg for more than 6 months. The virus can be transmitted from mother to child during or after birth (vertical transmission) or through direct contact with blood or body fluids from an infected person (horizontal transmission). Active infection can be categorised into two groups: HBeAg-positive and HBeAg-negative. In HBeAg-positive virus infection, the virus replicates and encodes infected liver cells to synthesise and secrete HBeAg. In contrast, the HBeAg-negative type is a variant form of HBV which can lead to productive viral infection without secretion of HBeAg. HBeAg-negative virus can either occur through direct infection or emerge late in the course of infection in individuals first infected with HBeAg-positive virus.

More than 350 million people worldwide are chronically infected with HBV making it the tenth leading cause of death worldwide[5]. In the UK, CHB affects approximately 180,000 people (0.3% of the population) and many experts believe the figure to be higher[6]. There are an estimated 7,700 new cases of CHB each year in the UK; 96% of these are UK immigrants from areas of high prevalence (Asia, Eastern Europe and Africa) where HBV is frequently transmitted from mother to child[6,7.] Transmission of this infection could be prevented through vaccination. After a call by the World Health Organization for the global introduction of vaccine prevention programmes by 1997, 82% of countries in the world had introduced universal HBV immunisation programs[8]. However, in the UK it is currently only offered selectively to healthcare workers, babies born to infected mothers and other selected high-risk groups[6].

4.1.2 Burden of disease

Individuals with CHB are at an increased risk of developing liver cirrhosis, hepatic decompensation (with consequent possible need for liver transplantation) and hepatocellular carcinoma (HCC). An estimated 15–40% of CHB patients will develop these serious sequelae and some will be potential candidates for liver transplantation [9] [10]. HBV infection accounts for up to 1.2 million deaths each year worldwide, furthermore, 25% of cases of HCC are due to chronic infection[11].

CHB infection is associated with negative impact on QoL, even in the absence of cirrhosis or cancer, and people with CHB attribute a wide range of negative psychological, social and physical symptoms to their condition[12]. Affected individuals may be concerned about the risk of liver damage and anxious about passing on the virus to other people, and their families may feel isolated and afraid. Furthermore, the QoL of people who progress to liver failure and primary liver cancer (HCC) is even more impaired[6].

Currently, there are no rigorous estimates of the economic burden imposed by HBV in the UK6. However, it is estimated that the management of HBV could potentially cost the NHS from £26 million to £380 million annually6. The total cost to the economy, including time lost at work, is likely to be substantially higher6. A study of Hepatitis B management costs in the UK [13] showed that the annual cost of the disease increased with disease severity. The average annual cost of CHB in 2001 increased from £1,305 to £1,457 and £5,822 in the compensated and

decompensated cirrhotic stages respectively. The annual cost of HCC was £6,146, and the annual cost of a liver transplant was £31,121. Numerous economic evaluations have demonstrated that early treatment of CHB reduces the costs associated with managing the associated complications, particularly cirrhosis and HCC6.

4.1.3 Treatment of chronic hepatitis B

4.1.3.1 Treatment goals

There are a growing number of therapies which can control CHB and prevent potentially fatal complications. The ultimate goals of therapy are to decrease the incidence of cirrhosis, end-stage liver disease (therefore avoiding consequential liver transplantation), HCC and liver-related mortality [5]. These long-term goals are difficult to evaluate in clinical trials, so a set of surrogate endpoints are used to assess treatment efficacy[14]. Measures of treatment response include decrease in serum HBV DNA level, HBeAg loss/seroconversion (in patients who were initially HBeAg positive), HBsAg loss/seroconversion, normalization of serum ALT and improvement in liver histology14. Clearance of HBsAg is the key objective; however this occurs only rarely and is of limited use as a treatment endpoint. Histological response, although an invasive measure, has often been used as the primary end point because it is considered an objective efficacy measure corresponding to the remission of liver disease14. Increasing evidence is emerging to establish HBV viral load as a valid predictor of CHB disease progression and it is now used both as a trigger for treatment initiation and as an indicator of treatment response. Therefore a recognised aim of treatment, in both HBeAg-positive and -negative patients, is to achieve sustained suppression of HBV replication, avoiding resistance, and remission of liver disease5. For HBeAg-positive patients, viral load reduction to undetectable DNA levels facilitates HBeAg seroconversion, which is an important measure of treatment response and can determine treatment discontinuation. For HBeAg-negative patients, in whom HBeAg loss is not applicable, the criteria for stopping antiviral treatment are less clear since viral replication can resume once treatment has ceased, even after an extended period of viral suppression[15].

4.1.3.2 Current treatment options and their limitations

Two main classes of drug are used in the treatment of CHB:

- Interferons (IFNs); these agents have both immunomodulatory and potentially direct antiviral properties.
- Nucleo(s/t)ide analogues (NAs); these directly suppress HBV replication, but indirect effects on immune response may be observed when viral titres are profoundly suppressed.

Interferons

IFNs are natural proteins that activate the immune system in response to viral infection, in addition to possessing other antiviral and antiproliferative effects[16]. At present, two recombinant IFNs and one pegIFN have UK marketing authorisation for the treatment of CHB. IFN-α was the first to be licensed in the UK and is administered as subcutaneous injection three times weekly[17]. PegIFN has a slower rate of absorption and excretion (due to the attachment of polyethylene glycol), which allows it to be injected once weekly. Treatment duration is limited to a designated 6- or 12-month course of therapy[18].

In HBeAg-positive patients treated with pegIFN for 48 weeks, clinical trials show that 32% of patients achieve sustained HBeAg seroconversion at 24 weeks post-therapy, with sustained HBV DNA suppression (<400 copies/mL) in 14% of patients[18 19]. In HBeAg-negative patients treated with pegIFN for 48 weeks, 19% achieve sustained HBV DNA suppression at 24 weeks post-therapy[20]. Thus, many patients do not achieve a sustained antiviral response post-treatment and may require additional treatment with NA therapies.

PegIFN therapy is poorly tolerated. Clinical trials showed 88% of patients reporting side effects after 48 weeks of treatment and 24-week post-treatment follow-up. Serious side effects were reported by 6% of patients, with 5% of patients withdrawing due to adverse events or laboratory abnormalities[18]. The most common side effects are an initial influenza-like illness with fever, chills, headache, malaise and myalgia. Other common side effects include fatigue, anorexia, weight loss and a mild increase in hair loss[18].

PegIFN therapy is also resource intensive since patients on treatment require frequent monitoring, with haematological and biochemical blood tests required every 2–4 weeks[18].

Because of its limited efficacy and sub-ptimal safety profile, pegIFN is considered suitable only for short-term but not long-term treatment of CHB.

Nucleo(s/t)ide analogues

NA antiviral agents act directly to inhibit viral replication. In addition to entecavir, there are three other NA antiviral agents licensed for the treatment of CHB in the UK; lamivudine, adefovir and telbivudine.

In HBeAg-positive patients, NA treatment is routinely administered until HBeAg seroconversion is achieved, with a further period of treatment for consolidation of response. However, the majority of patients do not undergo HBeAg seroconversion, which facilitates viral suppressioion, during short-term treatment with NAs. Thus, prolonged administration to maintain viral suppression is appropriate in most patients. Longer-term NA treatment is required in HBeAg-negative patients for whom the only agreed endpoint is serum HBsAg clearance, which only occurs rarely. There is currently no consensus around NA treatment duration in HbeAg-negative patients. Antiviral therapies are therefore prescibed either over a fixed duration or, more commonly, as long-term viral suppressive therapy5.

Although the majority of CHB patients require prolonged treatment with NAs, long-term treatment with all analogues can result in an increase in the selection and emergence of resistant HBV strains. Development of resistance carries the risk of exacerbation of hepatitis, disease progression and may also limit future treatment options[21 22]. Consequently, in selection of the optimal NA, a key treatment goal must be the avoidance of resistance, thus using wherever possible the most potent NA with the lowest rate of resistance[5].

The antivirals licensed for use in CHB patients in the UK are summarised below.

Lamivudine: Clinical trials show rates of viral suppression (solution hybridisation assay, lower level of detection <1.6 pg/mL) to be 34–57% in HBeAg-positive patients and 71% in HBeAg-negative patients after 1 year of treatment[23]. Lamivudine is generally well tolerated but its efficacy is limited by resistance, which is reported in 24% of patients after 1 year of therapy, increasing to 67% after 4 years[23]. In addition

to an increased risk of acute hepatic flare and disease progression, lamivudine resistance also allows the development of cross-resistance to telbivudine and reduced susceptibility to entecavir. Concerns about the risk of lamivudine resistance has now prompted recommendations that lamivudine no longer be considered the preferred option for first-line therapy[5].

Adefovir: The antiviral efficacy of adefovir appears to be lower than that of lamivudine. Clinical trials show rates of viral suppression (HBV DNA <400 copies/mL by PCR-based assay) to be 21% in HBeAg-positive patients and 51% in HBeAg-negative patients after 1 year[24]. Adefovir has also shown slow viral kinetics compared with entecavir[25]; in a head-to-head comparison between entecavir 0.5 mg and adefovir 10 mg in NA-naïve HBeAg-positive patients, entecavir was superior for the primary endpoint of viral load reduction at week 12 and a significant difference between the treatment arms in favour of entecavir was reached as early as day 1025. Resistance to adefovir has been reported in approximately 11% of HBeAg-negative NA-naïve patients after 3 years, increasing to 29% after 5 years24. Adefovir therapy is associated with a potential risk of nephrotoxicity and patients should be monitored for changes in serum creatinine every 3 months and creatinine clearance calculated24.

Telbivudine: Recently licensed, clinical trials show rates of viral suppression (HBV DNA <300 copies/mL by PCR-based assay) to be 60% in HBeAg-positive patients and 88% in HBeAg-negative patients after 1 year[26],[27]. Current rates of resistance at 2 years of treatment in NA-naïve patients are reported to be 22% for HBeAg-positive patients and 9% for HBeAg-negative patients[5]. Telbivudine is generally well tolerated. Current guidelines place it alongside lamivudine as a possible but not preferred option for treatment-naïve patients[5]

Entecavir: This will be discussed in the following sections.

4.1.3.3 Current treatment pathway

A 2006 NICE technology appraisal reviewed the use of adefovir and pegIFN for the treatment of CHB, at which time IFN-α, pegIFN, lamivudine and adefovir were licensed for the treatment of CHB4. NICE recommended the use of pegIFN as an option for first-line treatment, followed by lamivudine if needed4. Adefovir is recommended for lamivudine-resistant patients4. The NICE guidance, as it stands, allows for a number of treatment modifications to be made to the suggested guidelines.

The most recent CHB treatment guidelines are the US national guidelines published by the AASLD in 20075 and an American treatment algorithm published in 2007 by Keeffe et al.[28], both of which review all currently licensed CHB therapies. The most recent European guidelines (from the European Assocation for the Study of the Liver [EASL]) were published in 2003, but these did not consider entecavir, telbivudine or pegIFN as they were not licensed therapies at this time[29]. The UK currently has no national treatment guidelines for CHB.

The AASLD guidelines[5] and Keeffe et al.[28] do not recommend one specific therapy, instead leaving the choice between the available licensed options to the clinician's discretion. Preference is expressed for pegIFN, adefovir or entecavir for first-line therapy in HBeAg-positive and HBeAg-negative patients. Lamivudine and telbivudine

are not preferred due to high rates of resistance. Section 4.6 provides details of the guidelines.

For treatment-naïve CHB patients, market research suggests that, within the UK, there is limited use of pegIFN[30] and that lamivudine is the most widely used first-line therapy [30, 31]. For patients who do not respond to treatment with lamivudine alone, the data suggest that combination therapy with adefovir/lamivudine is most commonly used[30,31,] an option also endorsed by NICE[4].

4.1.3.4 Limitations of the current treatment pathway

Limitations of lamivudine as the most commonly used CHB therapy include suboptimal viral suppression and inadequate clinical efficacy in association with the early emergence of viral resistance, which if unmanaged, increases the risk of acute hepatic flare and disease progression[21 22]. Lamivudine resistance also potentially restricts future treatment options by allowing the development of cross-resistance to telbivudine and reduced susceptibility to entecavir. A key unmet medical need of current CHB treatment is therefore to achieve sustained viral response without the emergence of resistance. In selecting the appropriate CHB therapy, consideration should be given to the efficacy/potency profile relating to DNA suppression and to the risk of resistance.

4.2 What was the rationale for the development of the new technology?

ETV was developed to meet the unmet medical need for an antiviral agent that can provide HBV DNA suppression with minimal development of resistance and comprises the following features:

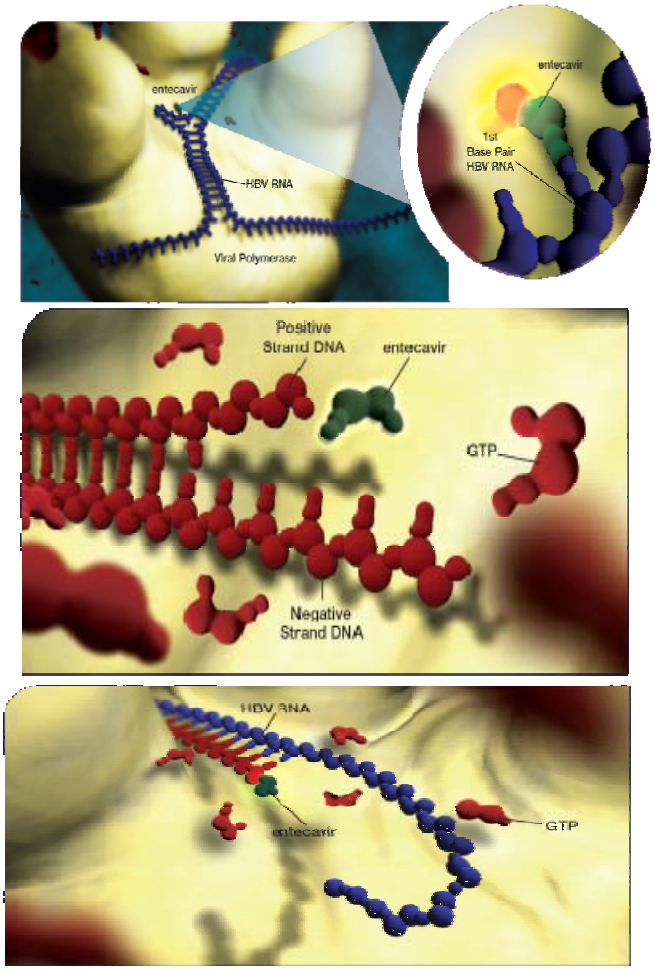
- Novel 3-step mechanism of action (as detailed in Section 4.3)
- Potent activity in vitro against wild-type and resistant strains of HBV; as reported in the SmPC, entecavir inhibits HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC_{50} value for entecavir against lamivudine-resistant HBV was 0.026 μM (range 0.010–0.059 μM). The potent antiviral activity of encetavir results in rapid viral suppression to undetectable HBV DNA levels[1].
- High genetic barrier; three or more viral mutations are required to cause resistance compared with competitors (which require only one)[32].
- High pharamacological barrier; large gap between the 50% inhibitory concentration (IC_{50}) and drug concentration[1].
- ETVr mutations lead to poor viral fitness with low replicative capacity[33].

The above features combine to provide entecavir with high potency and minimal risk of resistance, making it a good choice for the first-line treatment of NA-naïve CHB patients.

4.3 Principal mechanism of action of entecavir

Entecavir inhibits three distinct phases of HBV DNA replication: the HBV DNA polymerase base priming, the reverse transcription from the pregenomic messenger RNA and the synthesis of the positive strand of HBV DNA (Figure 4.1). Entecavir has a distinct mechanism of action causing delayed and nonobligate chain termination, in contrast to adefovir and lamivudine which cause an immediate chain termination.

Therefore, entecavir appears to act as a structural terminator, introducing structural distortion that prohibits optimal interaction between HBV DNA polymerase and the growing DNA chain[34 35].



Step 1: HBV DNA base priming

Step 2: Reverse transcription of the negative strand from the pregenomic messenger RNA

Step 3: Synthesis of the positive strand of HBV DNA

Figure 4.1: Mechanism of action of entecavir.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

It is proposed that entecavir be the first-line antiviral treatment for NA-naïve CHB patients (HBeAg-positive or -negative), within its licensed indications, because entecavir provides effective viral suppression with a very good long-term resistance profile which is associated with a proven clinical efficacy and an acceptable safety profile.

The NICE guidance recommends pegIFN as an option for initial treatment of adults with CHB, followed by lamivudine and then adefovir, with each sequential step occurring when the prior one has been unsuccessful[4]. In practice, in the UK, lamivudine is the most frequently used first-line treatment which predisposes patients to antiviral resistant mutations, resulting in the need for combination therapy in a substantial proportion of patients, and limiting future treatment options due to the development of cross-resistance or reduced susceptibility to other NAs.

In the US, recent AASLD guidelines[5] and a treatment algorithm by Keeffe et al.[28] recommend that selection of first-line therapy should be the choice of the most potent antiviral with the least potential for resistance, in order to achieve maximal viral suppression, thereby acknowledging the significance of viral load as the strongest determinant of CHB disease severity and progression. Evidence from clinical studies in treatment-naïve patients presented in this submission shows significant benefit for entecavir over lamivudine, with higher rates of viral suppression and lower rates of resistance. Entecavir therefore fills the unmet need of providing superior efficacy and a superior resistance profile.

It is proposed that entecavir should also be considered as a treatment option for patients with lamivudine resistance.

There is no direct clinical evidence comparing entecavir with current UK clinical practice. However, evidence from clinical studies presented in this submission shows that patients who do not respond to lamivudine would benefit from switching to entecavir. The AASLD guidelines recommend entecavir as a clinical option in this case, as an alternative to add-on adefovir.

4.5 Issues in current clinical practice, variations or uncertainty about best practice

The main issues in current clinical practice relate to the commonly used CHB treatments providing suboptimal viral suppression, inadequate clinical efficacy and early emergency of viral resistance. This results in a degree of uncertainty regarding current best practice which is reflected by changing patterns of care, continuing evolution of guidelines and the lack of consensus around treatment pathways.

4.5.1 CHB markers for disease progression and treatment outcome

Viral suppression is becoming increasingly accepted as an important marker of CHB.

There is an ongoing shift in understanding of the role of markers of viral replication such as HBV viral load and HBeAg as independent predictors of cirrhosis, HCC and mortality in people with CHB. The advent of new HBV quantification assays with improved sensitivity, standardised to a World Health Organization HBV reference, has allowed improved understanding. By linking serum HBV titre to the progression of liver disease, published studies show that patients with high HBV DNA levels have an increased risk of cirrhosis, HCC and liver-related death[36, 37, 38, 39].

The REVEAL–HBV (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–HBV) study – a 13-year prospective, population-based cohort study involving 23,820 Taiwanese subjects, including 3653 patients with CHB infection and a serum HBV DNA test at enrolment who were not co-infected with HCV, the largest natural history study of CHB patients to date – demonstrated a strong relationship between baseline viral load and the development of cirrhosis, HCC and mortality[40, 41, 42]. HCC incidence rates per 100,000 person-years increased from 145.2 among patients with undetectable HBV DNA (<300 copies/mL) at cohort entry to 1152 among those with a viral load of $\geq 10^6$ copies/mL. Compared to subjects with undetectable HBV DNA (<300 copies/mL) at cohort entry, the risk of HCC increased to 17.7 times higher for those subject with baseline viral load of $\geq 10^6$ copies/mL. The relationship between viral load and risk of HCC remained significant after adjustment for potentially confounding variables such as ALT and HBeAg status[36 43].

A recently published retrospective study conducted in Italy evaluated the correlation between viral load and disease progression in 70 untreated consecutive Caucasian patients over a 25-year period[44]. The results support the findings of the REVEAL, HBV study concluding that the risk of liver-related mortality in Caucasian adults with CHB is correlated with sustained disease activity and onging high level of HBV replication independently of HBeAg status.

Momméja-Marin et al. propose that, similar to the direct correlation between viral replication and disease progression during HIV and HCV infection, a correlation exists between viral replication and disease progression during HBV infection[45]. Their literature review and meta-analysis demonstrated statistically significant correlations between serum HBV titre and histological damage. They concluded that HBV viral replication is the disease and liver histological damage is the consequence of the disease, similar to HIV infection where viral replication is the disease and low CD4+ cell count is the consequence.

CHB infection is often a lifelong disease and it is hard to demonstrate clinically important benefits in clinical trials[14]. An exception is the evaluation of viral suppression in patients with established or imminent clinical complications. Placebo-controlled clinical trials in patients with decompensated cirrhosis or lamivudine resistance have shown that treatment with antivirals reduces viral load and brings about disease regression; Liaw et al. showed that treatment with lamivudine reduced the risk for decompensation in patients with compensated cirrhosis at baseline[46].

Long-term follow-up of patients attaining adequate control of viraemia with antiviral therapy is needed to build on this existing observation that therapy with antivirals also controls liver-related mortality from decompensated liver disease and HCC[15].

While viral load is emerging as a noninvasive marker for treatment initiation and disease/treatment monitoring, there is a degree of uncertainty over the value of other biochemical and serological markers.

4.5.1.1 ALT

ALT is routinely used as an indicator of liver inflammation, although its value as a reliable parameter for assessing CHB disease activity is questionable since patients with normal ALT levels are still at risk of liver disease[14 5]. Futhermore the debate continues over what should be considered the nrmal range for ALT. It is generally considered that the currently accepted upper limits of normal are too high, though consensus has yet to be reached on what values should be considered acceptable[28].

4.5.1.2 HBeAg seroconversion

HBeAg seroconversion was the primary surrogate endpoint evaluated in early clinical trials of CHB patients and is typically associated with diminished viral replication and reduced liver inflammation[14]. However there are a number of limitations to its use as a surrogate marker:

- Viral rebound can occur post-treatment; as a consequence, the AASLD guidelines recommend close monitoring of patients taken off treatment after HbeAg seroconversion[5].

- It is not a reliable marker for long-term improvement in disease, since even with sustained HBeAg-negativity, serum HBV DNA can rise and be associated with resumption of liver damage[47].

- HBeAg loss is not applicable to patients with HBeAg-negative disease where viral load is the key measure of response[5].

In a 2005 state of the art lecture by Lai, it was concluded that HBeAg seroconversion is not an adequate endpoint, more of a "way station" in the natural history of HBV infection, and the most important factor associated with development of cirrhosis complications and HCC is HBV viral load[48].

4.5.1.3 Histological improvement

Histological improvement, defined as a decrease in Histology Activity Index score by 2 points or more with no worsening of fibrosis is routinely used as a primary outcome measure in HBV clinical trials. The assessment of histological response is considered an objective efficacy variable as it corresponds to the ultimate goal of therapy, i.e. to induce remission of liver disease[14]. However, it is invasive and prone to sampling error and intra-observer variability. Nonetheless it continues to be used while alternative noninvasive biomarkers are being validated.

4.5.2 Uncertainties in the current UK treatment pathway

The main issues in current clinical practice relate to the most commonly used CHB treatments providing suboptimal viral suppression, inadequate clinical efficacy and early emergence of viral resistance. Consequently there is a degree of uncertainty regarding current best practice, reflected by changing patterns of care, continuing evolution of guidelines and a lack of consensus around treatment pathways.

The most commonly used treatment of NA-naïve CHB patients in the UK is lamivudine, followed by adefovir if treatment has been unsuccessful[30,31]. There are a number of uncertainties relating to this current treatment pathway.

4.5.2.1 The role of pegylated interferon

NICE guidance recommends pegIFN as an option for initial treatment[4]. However market research shows that in the UK only 8% of patients are started on IFNs (of which 85% receive pegIFN)[30]. PegIFN has been shown to be effective in suppressing HBV replication and in inducing remission of liver disease; however, its efficacy is limited to a small percentage of highly selected patients, depending on genotypic profile and type of infection (whether HBeAg-positive or -negative)[19 20 49]. Genotypes A and B have significantly better HBeAg clearance rates than are seen in the other genotypes[49].

Approximately one-third of HBeAg-positive patients will clear HBeAg after 6 or 12 months of pegIFN therapy[19]. The remaining two-thirds of patients who do not achieve seroconversion may need to be switched to long-term antiviral therapy. In HBeAg-negative patients with active disease, seroconversion cannot be used as a clinical endpoint and the role of pegIFN is less clear. Marcellin et al. report that 19% of HBeAg-negative patients achieve sustained viral suppression (HBV DNA <400 copies/mL) after 1 year of pegIFN therapy[20]. It has been proposed that in HBeAg-negative patients it may be more appropriate to initiate treatment with a nucleoside analogue rather than pegIFN[15].

4.5.2.2 Prevention versus management of resistance

The primary concern with the use of lamivudine as first-line therapy is the emergence of resistance, which is estimated to occur in 60–70% of cases after 5 years of treatment[5]. Development of lamivudine resistance increases the risk of disease progression and acute hepatic flare if left untreated. It also potentially restricts future treatment options by allowing the development of cross-resistance to telbivudine and reducing susceptibility to entecavir[21 22].

There are two treatment strategies to avoid drug resistance. Physicians can aim to minimise the risk of development of drug resistance in NA-naïve patients by selecting the most potent antiviral therapy with the least resistance for use as first line antiviral therapy. Alternatively, a rescue treatment strategy may be used (either switch or add-on) to manage the development of viral resistance to an agent with higher rates of resistance.

Current UK treatment practice is to manage the development of lamiduvine resistance with the use of adefovir as a rescue therapy. However, this practice is not evidence based, as only a minimal amount of data exists on the use of first-line and subsequent rescue NA therapy, with consequent uncertainty over optimal treatment strategies. Current UK practice is to use add-on adefovir, in preference to a switch[4].

The evidence supporting combination treatment over switch to adefovir in lamivudine-resistant patients is derived from small RCTs and uncontrolled observational data, largely in HBeAg-negative lamivudine-resistant patients [50, 51, 52, 53]. The results in HBeAg negative patients showed that LVD/ADV combination therapy had lower rates of resistance compared with a switch to adefovir. Lampertico et al. suggested that early intervention, when DNA levels are lower, was necessary to obtain the maximum benefit of rescue adefovir therapy[50]. However the requirement for early addition of adefovir demands more intensive patient monitoring to ensure timely intervention and results in long-term treatment of patients with combination therapy. The strategy of sequential add-on rescue therapy needs further supporting data to establish its role in the long-term management of all CHB[54].

The need to prevent resistance in treatment-naïve patients has been recognised in recently published guidelines[5]. These guidelines have indicated a preference for entecavir and adefovir over telbivudine and lamivudine due to their relative resistance profiles. The judicious use of NA in CHB patients appears to be the most effective prophylaxis to prevent multi-drug resistant HBV and to avoid the need for combination therapies. Among the approved NA therapies for CHB, entecavir is associated with the lowest rate of drug resistance in NA-naïve patients.

Given the above uncertainties, a technology which demonstrates effective viral suppression with an excellent long-term viral resistance profile, which is associated with proven clinical efficacy and an acceptable safety profile, should be chosen as the first-line treatment option.

4.6 Relevant guidelines or protocols

Issuing institution	Products referred to in guidelines	Guidelines
American Association for the Study of Liver Diseases (AASLD) Chronic hepatitis B Lok and McMahon 2007[5]	IFNα / pegIFNα Lamivudine Adefovir Tenofovir (+/– emtricitabine) Entecavir Telbivudine	**HBeAg-positive patients** • Treatment may be initiated with any of the six approved antiviral medications but pegIFNα, adefovir or entecavir are preferred. **HBeAg-negative patients** • Patients with serum HBV DNA >20,000 IU/mL and elevated ALT >2×ULN) should be considered for treatment. • Treatment may be initiated with any of the six approved antiviral medications but pegIFNα, adefovir or entecavir are preferred in view of the need for long-term treatment. **Patients with compensated cirrhosis** • Best treated with NAs because of the risk of hepatic decompensation associated with IFNα-related flares of hepatitis. In view of the need for long-term therapy, adefovir or entecavir is preferred. **Lamivudine-resistant patients** • Add adefovir or tenofovir. • Stop lamivudine, switch to tenofovir + emtricitabine. • Stop lamivudine, switch to entecavir (pre-existing lamivudine-resistant mutation predisposes to entecavir resistance)
Asia-Pacific Steering Committee Members ACT-HBV (Advancing the Clinical Treatment of Hepatitis B Virus) 2006[37]	Lamivudine Adefovir Entecavir IFNα / pegIFNα-2a Thymosin-α1	**HBeAg-positive patients** • Treatment may be initiated with IFNα, pegIFNα-2a, thymosin-α1, lamivudine, adefovir or entecavir. • For patients with ALT levels of >5×ULN, lamivudine or entecavir is recommended due to their greater suppressive effects and rapidity of action

Issuing institution	Products referred to in guidelines	Guidelines
		HBeAg-negative patients • Adefovir, entecavir, pegIFNα-2a, and interferon a are all preferred choices over lamivudine as first-line therapy because of the high rate of drug resistance seen with lamivudine. • Thymosin-α1 may also be used, particularly if the patient cannot tolerate IFN. **Patients with compensated cirrhosis** • Lamivudine, adefovir, entecavir and IFN (finite course) are considered first-line options. For long-term treatment, adefovir or entecavir is preferred over lamivudine. **Lamivudine-resistant patients** • Add adefovir and continue lamivudine for at least 3 months. • Switch to entecavir monotherapy in patients with compensated disease.
A treatment algorithm for the management of chronic hepatitis B virus infection in the United States Keeffe et al. 2006[28]	IFNα / pegIFNα-2a Lamivudine Adefovir Tenofovir (+/– emtricitabine) Entecavir	**HBeAg-positive patients** • Adefovir, entecavir or pegIFNα-2a are preferred first-line options. • Lamivudine is not considered a reasonable treatment option because of the high risk for resistance with long-term therapy and proven inferiority to pegIFNα-2a and entecavir in RCTs. **HBeAg-negative patients** • Adefovir, entecavir or pegIFNα-2a are preferred first-line options. • Lamivudine is not considered a reasonable treatment option because of the high risk for resistance with long-term therapy, and proven inferiority to peginterferon alfa-2a and entecavir in RCTs. **Patients with compensated cirrhosis** • Patients with HBV DNA <2000 copies/mL may be treated or observed. If treat, adefovir or entecavir preferred. • Adefovir or entecavir are first-line treatment options in patients with HBV DNA ≥2000 copies/mL.

Issuing institution	Products referred to in guidelines	Guidelines
		Lamivudine-resistant patients • Add adefovir (may be preferred over a switch to adefovir). • Switch to entecavir (risk for subsequent entecavir resistance). • Potential future management: add tenofovir or switch to emtricitabine/tenofovir.

ALT: alanine aminotransferase; HBV: hepatitis B virus; IFN: interferon; pegIFN: pegylated IFN; RCTs: randomised controlled trials; ULN: upper limit of normal.

5 Clinical evidence

5.1 Identification of studies

The following clinical evidence collection strategy was used:

I. Evidence was collected to demonstrate the safety and efficacy of the intervention, entecavir, in the management of patients with CHB.

II. The search strategy adopted by SHTAC[55] as part of NICE technology appraisal 96[4] was adapted and a search conducted during September 2007. MEDLINE, EMBASE and internal company databases were included in the search; however, the full range of databases searched by SHTAC was not utilised due to limitations in accessing the databases. Searches were not limited by date but were restricted to English-language results. Search terms can be found in Appendix 8.2 and 8.3.

III. The search results were sorted to identify RCTs providing clinical evidence of the comparative efficacy and safety of entecavir with other therapies (including placebo) in patients with CHB.

5.2 Study selection

5.2.1 Complete list of RCTs

A complete list of RCTs comparing entecavir with other therapies (including placebo) in the relevant patient groups is shown in Table 5.1.

Table 5.1: Complete list of randomised controlled trials comparing entecavir with other therapies

	Trial no.	Drug dosages	Comparator	Population	Design	Duration	Objectives
1	**004**	Entecavir 0.05, 0.1, 0.5, 1.0 mg qd	Placebo	CHB patients	Dose-ranging, randomised, double-blind, placebo-controlled	28 days	Dose selection; safety and efficacy versus placebo
2	**005**	Entecavir 0.05, 0.1, 0.5, 1.0 mg qd; lamivudine 100 mg qd	Lamivudine	CHB patients	Dose-ranging, randomised, double-blind, active comparator	24 weeks (with 12-week follow-up post-treatment in responders)	Dose selection; safety and efficacy versus lamivudine
3	**012**	Entecavir 0.05, 0.1, 0.5, 1.0 mg qd; lamivudine 100 mg qd	Placebo	CHB patients, Chinese	Two-dose comparison, randomised, double-blind, placebo-controlled	4 weeks (with 8-week follow-up post-treatment); 48-week, open-label entecavir 0.5 mg extended dosing	Dose selection; safety and efficacy versus placebo in Chinese population
4	**014**	Entecavir 0.1, 0.5, and 1.0 mg qd; lamivudine 100 mg qd	Lamivudine	CHB patients with recurrent viraemia on lamivudine	Dose-ranging, randomised, double-blind, active comparator	52 weeks (with extended open-label entecavir 1.0 mg treatment for partial virological response at 48 weeks)	Dose selection; safety and efficacy versus lamiduvine
5	**022**	Entecavir 0.5 mg qd; lamivudine 100 mg qd	Lamivudine	NA-naïve, HBeAg-positive CHB patients	Randomised, double-blind, active comparator	52 weeks (with 24-week follow-up post-treatment); Virological-only responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first.	Safety/efficacy of entecavir in HBeAg-positive patients versus lamiduvine

6	**023**	Entecavir 0.5 mg qd; lamivudine 100 mg qd	Lamivudine	HBeAg-positive and -negative, Chinese CHB patients	Randomised, double-blind, active comparator	52 weeks; patients with consolidated response were followed for 24 weeks; partial responders continued blinded treatement in second year; nonresponders who discontinued drug could be followed for 24 weeks or enroll in a rollover study	Safety/efficacy of entecavir in HBeAg-positive and -negative Chinese patients versus lamivudine
7	**026**	Entecavir 1.0 mg qd; lamivudine 100 mg qd	Lamivudine	Lamivudine-refractory, HBeAg-positive CHB patients	Randomised, double-blind, active comparator	52 weeks (with 24-week follow-up post-treatment). Virological-only responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first.	Safety/efficacy of entecavir in lamivudine-refractory HBV or incomplete response versus lamivudine
8	**027**	Entecavir 0.5 mg qd; lamivudine 100 mg qd	Lamivudine	NA-naïve, HBeAg-negative CHB patients	Randomised, double-blind, active comparator	52 weeks (with 24-week follow-up post-treatment). Virological-only responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first.	Safety/efficacy of entecavir in HBeAg-negative patients versus lamivudine
9	**038**	Entecavir 1.0 mg qd	Placebo	HIV/HBV co-infected patients already receiving NA therapy and have recurrence of HBV	Randomised, double-blind, placebo controlled	48 weeks	Safety/efficacy of entecavir in HIV/ HBV co-infected population versus placebo

10	**047**	Entecavir 0.01, 0.1 and 0.5 mg qd; lamivudine 100 mg qd	Lamivudine	CHB, lamivudine-naïve, Japanese patients	Dose-ranging, randomised, double-blind, active comparator	24 weeks	Efficacy/safety in lamivudine-naïve Japanese patients versus lamivudine
11	**056**	Entecavir 1.0 mg qd	Placebo	CHB Chinese patients who have failed lamivudine	Randomised, double-blind, placebo controlled	12 weeks followed by optional open-label entecavir 1.0 mg treatment for 36 weeks	Safety/efficacy of entecavir in Chinese patients who have failed lamivudine versus placebo
12	**079**	Entecavir 0.5 mg qd; adefovir 10 mg qd	Adefovir	HBeAg-positive, NA-naïve CHB patients	Randomised, open-label, active comparator	52 weeks minimum, 96 weeks maximum	Efficacy of entecavir versus adefovir in early viral load reduction

CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; qd: once daily.

5.2.2 Inclusion and exclusion criteria

The following inclusion criteria were applied in the systematic review to identify the studies detailed in the list of relevant RCTs (see Section 5.2.3) that address the decision problem:

- Published RCTs where the full paper can be obtained (studies with only abstracts available were excluded). Note studies undertaken by Bristol Myers-Squibb but not yet published were included where the completed clinical study report was available.
- Patients in at least one arm of the trial must receive entecavir alone, as in the proposed indication. Comparators for the treatment of treatment-naïve patients were lamivudine, pegIFNα-2a and telbivudine. The comparator for the treatment of lamivudine-resistant patients was ADV/LVD combination. Placebo (including the 'do nothing' option) or standard care were included as comparators for both NA-naïve and refractory patients, unless a clinical trial with a relevant active comparator was included, in which case such studies were excluded.
- Head-to-head trials were included.
- The patients of interest were adults with compensated liver disease and active CHB who are either HBeAg-positive or -negative.
- Long-term extension studies of observational design were included (see Section 5.2.4).

The following exclusion criteria were applied in the systematic review:

- Non-randomised or uncontrolled studies (unless these are long-term extensions of RCTs), observational studies, case series, letters to editor, studies without abstracts, studies published as abstracts only.
- Reviews were analysed for the purpose of checking the bibliographies, but were excluded from the list of included studies.
- Trials in diseases other than CHB.
- Studies where patients had decompensated liver disease in conjunction with CHB were excluded as entecavir is not indicated for treatment at this stage.
- Studies where patients were co-infected with an additional virus (e.g. HIV as the scope of this submission does not specifically consider people with CHB known to be co-infected with HIV).
- Studies investigating the treatment of CHB post-liver transplant.
- Given the availability of large studies with duration of 48 weeks or more, shorter studies were excluded on the basis that insufficient time would have elapsed to accurately detect endpoints such as seroconversion of HBeAg-positive patients.
- Non-English-language publications were excluded.

5.2.3 List of relevant RCTs

Table 5.2: Relevant RCTs evaluating the safety and efficacy of entecavir in the management of CHB

The methodology and results of these studies are presented in Sections 5.3 and 5.4, respectively.

	Trial No	Drug Dosages (bold indicates licensed entecavir dose in the UK)	Comparator	Population	Design (number of patients)	Duration	Trial dates *	Primary study ref/CSR
1	**022**	Entecavir **0.5 mg qd**; lamivudine 100 mg qd	Lamivudine	NA-naïve, HBeAg-positive, CHB patients	Randomised, double-blind, active comparator (n=715)	52 weeks (with 24-week follow-up post-treatment). Partial virolgical responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first	10 May 2001 – 10 Feb 2005	Chang et al. 2006[56] CSR[57] SmPC[1]
2	**027**	Entecavir **0.5 mg qd;** lamivudine 100 mg qd	Lamivudine	NA-naïve, HBeAg-negative CHB patients	Randomised, double-blind, active comparator (n=648)	52 weeks (with 24-week follow-up post-treatment). Partial virological responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first	28 Nov 2001 – 25 May 2005	Lai et al. 2006[58] CSR[59] SmPC[1]
3	**023**	Entecavir **0.5 mg qd**; lamivudine 100mg qd	Lamivudine	HBeAg-positive and -negative Chinese CHB patients	Randomised, double-blind, active comparator (n=525)	52 weeks (with 24-week follow-up post-treatment). Patients with a consolidated response were followed for 24 weeks; partial responders continued blinded treatment in second year; nonresponders discontinued drug could be followed for 24 weeks or enroll in a rollover study	10 Jul 2003 – 10 Feb 2006	Yao et al. 2007[60] CSR[61]
4	**026**	Entecavir **1.0 mg qd**; lamivudine 100 mg qd	Lamivudine	Lamivudine-refractory, HBeAg-positive CHB patients	Randomised, double-blind, active comparator (n=293)	52 weeks (with 24-week follow-up post-treatment). Partial virological responders at 48 weeks were able to continue blinded study medication until week 96 or until a response was achieved, whichever came first	01 Dec 2001 – 01 Apr 2005	Sherman et al. 2006[62] CSR[63] SmPC[1]
5	**014**	Entecavir 0.1, 0.5, **1.0 mg qd**; lamivudine 100 mg qd	Lamivudine	CHB patients with recurrent viraemia on lamivudine	Dose-ranging; randomised, double-blind, active comparator (n=182)	52 weeks (with extended open-label entecavir 1.0 mg treatment for patients with a partial virological response at 48 weeks)	05 Apr 2000 – 15 Jan 2004	Chang et al. 2005[64] CSR[65]

* Start date represents the first visit in the first patient; end date represents the last visit in the last patient.
CHB: chronic hepatitis B; CSR: clinical study report; HBeAg: hepatitis B e antigen; NA: nucleo(s/t)ide analogue; qd: once daily.

5.2.4 List of relevant non-RCT evidence

Table 5.1: List of relevant non-RCT evidence

Trial no.	Drug dosages (bold indicates licensed dose in the UK)	Population	Design / duration	Justification for inclusion	Trial dates Start (FPFV)-Finish (LPLV) [CSR]	Primary study ref.
901 - 4 year treatment cohort (022 extension)	In 022: entecavir **0.5mg** In 901; Entecavir 1 mg (Entevavir 1mg plus lamivudine 100mg)	Entecavir-treated NA-naïve HBeAg positive CHB patients from 022	Open-label / 144 weeks	Long-term cohort of patients treated with entecavir	9 Jan 01	Han et al. 2007[66]
Entecavir 4-year resistance monitoring programme	In RCTs; Entecavir **0.5** mg or **1.0 mg** In study 901: - Entecavir **0.5mg** + lamivudine 100 mg - Entecavir **1mg** + lamivudine 100 mg, - Entecavir **1.0 mg** only	NA-naïve and LVD-refractory CHB patients treatedvwith entecavir in RCTs and 901	Observational	Long-term resistance data	–	Internal report[67] Colonno et al. 2007[68];

CHB: chronic hepatitis B; CSR: clinical study report; FPFV: first patient first visit; LPLV: last patient last visit; qd: once daily.

The methodologies and results of these studies are presented in Section 5.8.

5.2.5 Ongoing studies

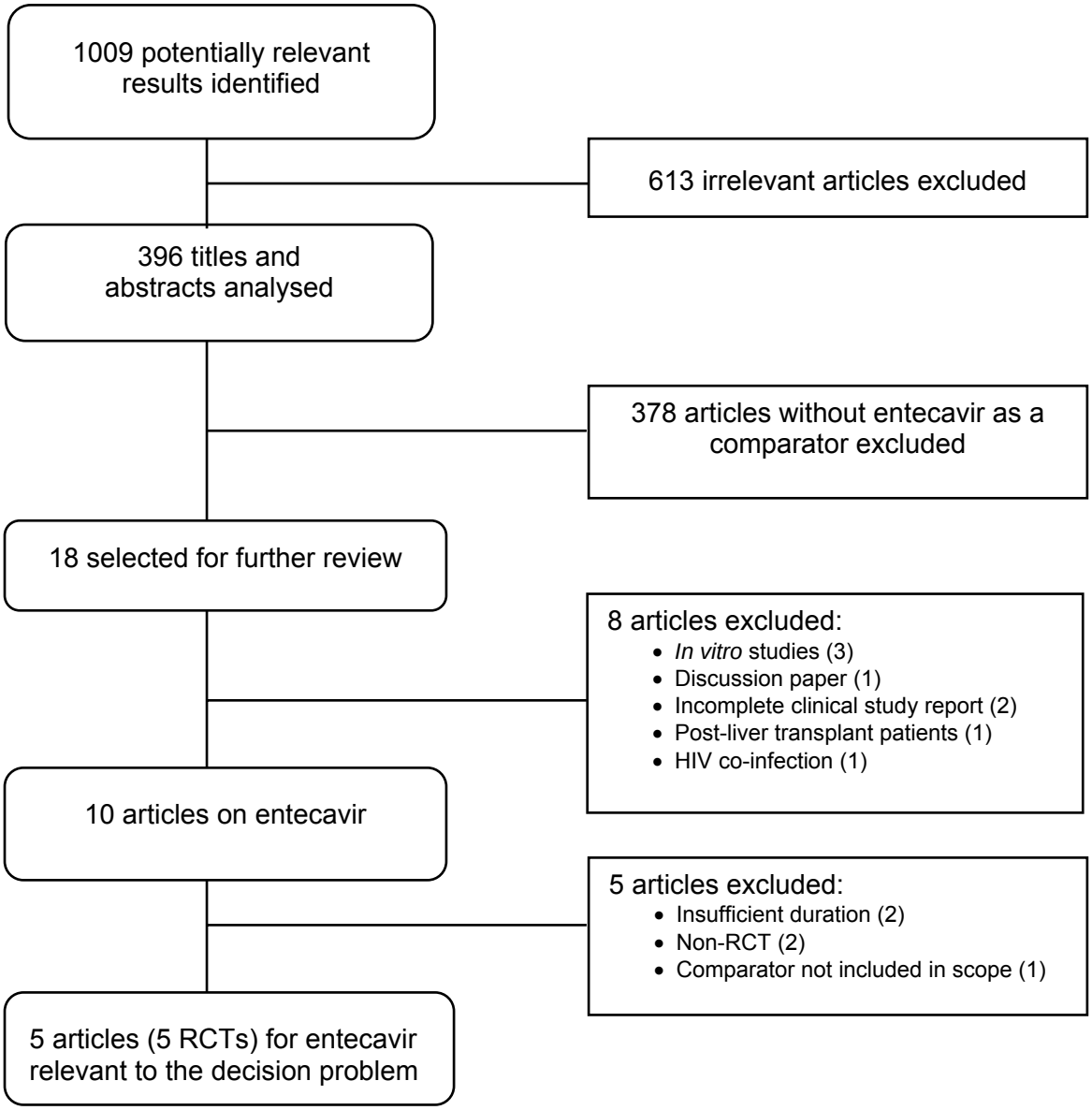
Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

Table 5.4: List of ongoing studies

Trial no.	Drug dosages (bold indicates licensed dose in the UK)	Comparator	Population	Duration	Double-blind or open-label trial	Study start (FPFV)
901	Entecavir **1 mg**	None	NA-naïve HBeAg-positive CHB patients	5 years	Open-label extension of AI463-022	9 Jan 01
901	Entecavir **1 mg**	None	NA-naïve HBeAg-negative CHB patients	2+3 year re-treatment cohort	Open-label extension of AI463-027	9 Jan 01
901	Entecavir **1 mg**	None	NA-naïve, HBeAg-positive and -negative CHB patients	Long-term histology	Open-label extension of AI463-022 and AI463-027	9 Jan 01
Entecavir resistance cohort	Entecavir **0.5** and **1 mg**	None	NA-naïve and lamivudine refractory CHB patients	5 years	Cohort analysis	-
023/050	Entecavir **1 mg**	None	NA-naïve HBeAg-positive or -negative Chinese CHB patients	3 years	Open-label extension of AI463-023	17 May 04

CHB: chronic hepatitis B; FPFV: first patient, first visit; HBeAg: hepatitis B e anigen

5.2.6 QUORUM statement flow diagram of RCT selection



5.3 Summary of methodology of relevant RCTs

Summary data on the methodology of the relevant RCTs selected in the systematic review are presented in tabular form below. Details of methodology presented for each RCT include:

- Section 5.3.1: Methods (duration, blinding, randomisation, interventions, description)
- Section 5.3.2: Participants (inclusion, exclusion, baseline characteristics)
- Section 5.3.3: Patient numbers (numbers enrolled/randomised/treated, patients excluded after start of treatment, locations of centres and CONSORT flow charts)
- Section 5.3.4: Outcomes (primary and secondary outcomes investigated, validity of outcomes and measures)
- Section 5.3.5: Statistical analysis and definition of study groups (hypotheses, statistical analysis, sample size calculation, data management and patient withdrawals)
- Section 5.3.6: Critical appraisals

Data come primarily from the publication for each study. Where further detail was required, this has been obtained from the clinical study report, and this is specifically indicated and referenced. All references, including extracts from clinical study reports, are provided with this submission.

The validity of the outcomes, their relevance to the decision problem and acceptance by independent institutions and experts, or recommendations of such outcomes and measures are detailed in Section 5.3.4.

Discrepancies in sample sizes between publications and clinical study reports may occur due to retrospective updating of databases over time, and due to changes in Medical Dictionary for Regulatory Activities (MedDRA) classification.

5.3.1 Methods

RCT	Title	Intervention / duration	Population	Study type	Randomisation
022[56]	A Phase 3 study of the safety and antiviral activity of entecavir versus lamivudine in adults with CHB infection who are positive for HBeAg	Eligible subjects were randomised to receive either entecavir 0.5 mg qd or lamivudine 100 mg qd for a minimum of 52 weeks. At this time; subjects who demonstrated complete virological response (undetectable HBV DNA by bDNA assay and undetectable HBeAg) at week 48 discontinued study therapy and were followed off therapy for 24 weeks; partial virological responders (undetectable HBV DNA by bDNA assay but detectable HBeAg) continued therapy until 96 weeks or until complete virological response was achieved and then were followed off therapy for 24 weeks. Subjects who were virological nonResponders (detectable HBV DNA by bDNA assay) at week 48 discontinued therapy and had the option of enrolling in a separate Bristol Myers-Squibb "rollover" study. Subjects who elected not to enroll in another study were to be followed for safety every 4 weeks for 24 weeks in the current study after discontinuation of study therapy[56].	HBeAg-positive, nucleoside-naive CHB patients with compensated liver function[56].	Phase 3, multinational, multicentre, two-arm, double-blind, double-dummy RCT[56].	Eligible subjects were randomised (1:1) in a double-blind manner to receive either entecavir 0.5 mg qd or lamivudine 100 mg qd for a minimum of 52 weeks. A randomised block design with stratification by study site was used. Randomisation schedules were used in IVRS[56].
027 [58 59]	A Phase 3 study of the safety and antiviral activity of entecavir versus lamivudine in adults with CHB infection who are negative for HBeAg	Patients received entecavir 0.5 mg qd or lamivudine 100 mg qd for a minimum of 52 weeks. Patients who had a response (defined by an HBV DNA level <0.7 MEq/ml according to branched-chain DNA assay and an ALT level <1.25×ULN) or a nonresponse (defined by an HBV DNA level ≥0.7 MEq/mL) were to discontinue study treatment. Patients who had a response at week 48 and discontinued treatment were followed for 24 weeks after the cessation of treatment. Patients who had only a virological response (defined by an HBV DNA level <0.7 MEq/mL and an ALT level of at least 1.25×ULN) were offered continued therapy for up to 96 weeks[58].	HBeAg-negative NA-naïve CHB patients with compensated liver function[58].	Phase 3, multinational, multicentre, two-arm, double-blind, double-dummy RCT[58].	At the end of the screening period, eligible subjects were randomised (1:1) in a double-blind manner to receive either entecavir 0.5 mg qd or lamivudine 100 mg qd. A randomised block design stratified by study site was used[59].

023[60]	A Phase 3 study in China of the safety and antiviral activity of entecavir versus lamivudine in adults with CHB infection	Eligible subjects were randomised to receive either entecavir 0.5 mg qd or lamivudine 100 mg qd for up to 96 weeks. Patients achieving a consolidated response at week 48 discontinued study drug at week 52 and were followed for 24 weeks off-treatment. Patients who achieved a partial response at week 48 (HBV DNA <0.7 MEq/mL by bDNA assay but not yet meeting criteria for a consolidated response) were eligible to continue blinded treatment in the second year of the study. Virological nonresponders at week 48 (HBV DNA ≥0.7 MEq/mL by bDNA) were to discontinue study drug at week 52 and could either enroll in an entecavir rollover study or be followed for 24 weeks post-dosing and begin marketed anti-HBV therapy as recommended by their physician[60].	HbeAg-positive and –negative, NA-naïve CHB patients with compensated liver disease[60].	Phase 3, multicentre, two-arm, double-blind, RCT in Chinese patients[60].	Randomisation was performed centrally and stratified by HBeAg status and investigative site[60].
026 [62]	A comparison of entecavir to lamivudine in CHB patients with incomplete response to current lamivudine therapy	Patients received entecavir 1 mg qd or continued lamivudine 100 mg qd for a minimum of 52 weeks. At this time; subjects who demonstrated complete Virologic response (undetectable HBV DNA by bDNA assay and undetectable HBeAg) at week 48 discontinued study therapy and were followed off therapy for 24 weeks; partial virological responders (undetectable HBV DNA by bDNA assay but detectable HBeAg) continued therapy until 96 weeks or until complete virological response was achieved and then were followed off therapy for 24 weeks. Subjects who were virological nonresponders (detectable HBV DNA by bDNA assay) at week 48 discontinued therapy, and had the option of enrolling in a separate Bristol Myers-Squibb "rollover" study, subjects who elected not to enroll in another study were to be followed for safety every 4 weeks for 24 weeks in the current study after discontinuation of study therapy[62].	HBeAg-positive CHB patients with compensated liver function who were refractory to lamivudine therapy[62].	Phase 3, multinational, multicentre, two-arm, double-blind, double-dummy RCT[62].	Randomisation was accomplished using blocks of permuted treatment assignments and was stratified by study site[62].
014 [64]	A randomised, double-blind comparison of three doses of entecavir versus lamivudine in immunocompetent subjects with CHB infection with viremia on lamivudine therapy	Patients received either entecavir (0.1 mg, 0.5 mg or 1.0 mg qd) or continued with lamivudine therapy qd for up to 76 weeks. Decisions were made at week 28 of blinded dosing based on the virological response at week 24, and at week 52 of blinded dosing based on the response at week 48. Subjects who achieved a virological response at week 24 (≥1 $\log_{10}$ reduction in HBV DNA by bDNA assay compared with baseline levels) continued blinded therapy to week 52. Subjects who demonstrated only minimal virological response (<1 $\log_{10}$ reduction in HBV DNA and ≥ 10 MEq/mL by bDNA assay) at week 24 discontinued	Immunocompetent adult patients with CHB infection with viraemia on lamivudine therapy[64].	Phase 2, multinational, multicentre, four-arm, double-blind, randomised, controlled trial[64].	Eligible subjects were randomised 1:1:1:1 to one of three doses of entecavir (0.1, 0.5 or 1.0 mg qd) or to continued lamivudine therapy (100 mg qd). Subjects were randomised using IVRS. Randomisation was stratified by site. Subjects were to receive the first dose of study medication

		blinded study medication and either started alternative HBV therapy or were enrolled into the Bristol Myers-Squibb rollover study of entecavir plus lamivudine combination therapy (study AI463-901). Subjects who achieved a complete response at week 48 (HBV DNA < LLOQ by bDNA assay, loss of HBeAg and normal ALT for subjects positive for HBeAg at baseline; HBV DNA < LLOQ by bDNA assay, maintenance of negative HBeAg and normal ALT for subjects negative for HBeAg at baseline) discontinued study therapy and were followed off treatment for up to 24 weeks to assess the safety and durability of response. Subjects who demonstrated a partial response at week 48 (HBV DNA < LLOQ by bDNA but positive for HBeAg or abnormal ALT) continued blinded therapy for up to an additional 24 weeks (total of 76 weeks) or until they were enrolled into the open-label phase of this study. Subjects who did not demonstrate response at week 48 (HBV DNA ≥ LLOQ by bDNA assay) were to be discontinued from blinded treatment. These non-responders and subjects who had a relapse off treatment (HBV DNA ≥LLOQ by bDNA assay, or HBeAg positive, or ALT >1.5×ULN on two determinations at least 2 weeks apart after achieving complete response) could either enroll in study AI463-901 or start alternative anti-HBV therapy recommended by their physician[64].			within 72 hours of randomisation[64].

ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHB: chronic hepatitis B; CSR: clinical study report; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; IVRS: Interactive Voice Response Systems; LLOQ: lower limit of quantification; qd: once daily; RCT: randomised controlled trial; ULN: upper limit of normal range.

5.3.2 Participants

RCT	Inclusion criteria	Exclusion criteria	Baseline characteristics			
022[56]	Eligible patients were 16 years of age or older and had HBeAg-positive CHB and compensated liver function (total serum bilirubin ≤2.5 mg/dL [42.8 µmol/L]; PTT not >3 s longer than normal or an INR ≤1.5; serum albumin ≥3.0 g/dL; no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable HBsAg for ≥24 weeks before screening, evidence of CHB on a baseline liver-biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any commercial assay at least 4 weeks before screening, an HBV DNA level of ≥3 MEq/mL by the bDNA assay at screening, and a serum ALT level 1.3–10.0×ULN at screening[56].	Exclusion criteria included coinfection with hepatitis C, hepatitis D or HIV; the presence of other forms of liver disease; use of IFNα, thymosin-α, or antiviral agents with activity against hepatitis B within 24 weeks before randomisation; prior lamivudine therapy lasting >12 weeks; AFP >100 ng/mL; a history of ascites requiring diuretics or paracentesis; and previous treatment with entecavir[56].	The two treatment groups were balanced at baseline			
			Criteria[56]		**Entecavir 0.5mg N=354**	**Lamivudine 100 mg N=355**
			Age (years) mean (±SD)		35 (13)	35 (13)
			Gender (% male)		274 (77)	261 (74)
			Adequate baseline biopsy specimen with Knodell necroinflammatory score ≥2 (n)		314	314
			Knodell necroinflammatory score, mean (±SD)		7.8 (2.98)	7.7(2.99)
			HBV DNA by PCR log_{10} copies/mL, mean (±SD)		9.62 (2.01)	9.69 (1.99)
			ALT (U/L), mean (±SD)		140.5 (114.3)	146.3 (132.3)
			Viral genotype n (%)	A	94 (27)	100 (28)
				B	68 (19)	77 (22)
				C	111 (31)	90 (25)
				D	37 (10)	49 (14)
				F	20 (6)	12 (3)
				other, indeterminate or missing	24 (7)	27 (8)
027 [58]	Eligible patients were aged ≥16 years and had HBeAg-negative CHB and compensated liver function (a total serum bilirubin level of 2.5 mg/dL [42.8 µmol/L] or less; PTT not >3 s longer than normal or an INR not >1.5; serum albumin ≥3.0 g/dL; no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable HBsAg for at least 24 weeks before screening, evidence of CHB on a baseline liver biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any	Co-infection with hepatitis C, hepatitis D or HIV; the presence of other forms of liver disease; use of IFNα, thymosin-α, or antiviral agents with activity against hepatitis B within 24 weeks before randomisation; previous lamivudine therapy lasting >12 weeks; AFP >100 ng/mL; a history of ascites requiring diuretics or paracentesis; and previous	**Criteria**[58]		**Entecavir 0.5 mg N=325**	**Lamivudine 100 mg N=313**
			Age (years) mean (±SD)		44 (11)	44 (11)
			Gender (% male)		248 (76)	236 (75)
			Adequate baseline biopsy specimen with Knodell necroinflammatory score ≥2 (n)		296	287
			Knodell necroinflammatory score, mean (±SD)		8.0 (2.7)	7.7 (2.8)
			Ishak fibrosis score, mean (±SD)		2.4 (1.2)	2.5 (1.3)

	commercial assay at least 2 weeks before screening, undetectable HBeAg, detectable anti-HBe, a serum HBV DNA level of at least 0.7 MEq/mL according to bDNA assay at screening, and a serum ALT level 1.3–10.0×ULN at screening[58].	treatment with entecavir[58].	HBV DNA by PCR log_{10} copies/mL, mean (±SD)		7.6 (1.8)	7.6 (1.7)
			ALT (U/L), mean (±SD)		141.0 (114.7)	143 (119.4)
			Viral genotype n (%)	A	33 (10)	33 (11)
				B	46 (14)	60 (19)
				C	57 (18)	51 (16)
				D	157 (48)	135 (43)
				F	32 (10)	34 (11)
				other, indeterminate or missing	33 (10)	33 (11)

023[60]	Eligible patients were ≥16 years of age and had a documented history of CHB infection (HBsAg-positive for ≥6 months) and compensated liver disease (total bilirubin ≤2.5 mg/dL, INR ≤1.5, serum albumin ≥3.0 g/dL, and no current evidence or history of variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis). Eligible patients also had a serum HBV DNA level ≥3.0 MEq/mL by bDNA assay at screening and evidence of HBV DNA by any commercial assay ≥12 weeks prior to screening, and ALT levels 1.3–10×ULN at screening and at least once ≥12 weeks prior to screening. Patients with either HBeAg-positive or -negative disease were eligible[60].	Exclusion criteria included the following: co-infection with hepatitis C virus, hepatitis D virus or HIV; other forms of liver disease; >12 weeks of therapy with an NA with activity against HBV; and therapy with any anti-HBV drug within 24 weeks prior to randomisation. During the study patients were not allowed to use traditional Chinese medicines and other herbal medicines intended to improve or protect liver function, or improve or prevent fibrosis[60].	**Criteria**[60]	**Entecavir 0.5 mg (N=258)**		**Lamivudine 100 mg (N=261)**	
				HBeAg + n=225	**HBeAg – n=33**	**HBeAg + n=221**	**HBeAg – n=40**
			Age (years) mean (±SD)	30 (9)		30 (9)	
			Gender (% male)	211 (82)		217 (83)	
			HBV DNA by PCR log_{10} copies/mL, mean (±SD)	8.64 (0.99)		8.48 (1.12)	
				8.77(0.86)	7.70(1.28)	8.65(1.0)	7.59(1.33)
			ALT (U/L), mean (±SD)	196 (140)		198 (180)	
				191(135)	225(169)	204(192)	164(83)
			Prior IFNα therapy, n (%)	37(14)		42(16)	

026 [62]	Eligible patients included HBsAg-positive men and women aged ≥16 years who were receiving ongoing lamivudine therapy and were refractory to that therapy. This was defined as any of the following: persistently detectable HBV DNA by bDNA assay after at least 36 weeks of lamivudine treatment; recurrence of detectable HBV DNA by bDNA assay on two determinations after achieving undetectable HBV DNA (by bDNA assay) on lamivudine; recurrence and persistence of HBV replication after discontinuing	Coinfection with hepatitis C, hepatitis D or HIV; other forms of liver disease; prior therapy with an NA with activity against HBV other than lamivudine for >12 weeks duration or given within 6 months prior to randomisation; use of IFNα, or thymosin-α1 within 6 months prior to randomisation; AFP >100 ng/mL; and prior treatment with entecavir[62].	**Criteria**[62]	**Entecavir 1 mg (N=141)**	**Lamivudine 100 mg (N=145)**
			Age (years) median (range)	38 (16–74)	40 (17–70)
			Gender (% male)	105 (74)	112 (77)
			Adequate baseline biopsy specimen with Knodell necroinflammatory score >2 (n)	124	116
			Knodell necroinflammatory score, mean (±SD)	6.5 (3.23)	6.5 (3.41)

	lamivudine provided that lamivudine had been reintroduced and maintained for ≥12 weeks prior to screening; or documented YMDD mutation and HBV viremia on lamivudine regardless of duration of therapy. Patients were HBeAg-positive and had ALT levels 1.3–10×ULN and HBV DNA levels ≥3.0 MEq/mL by Quantiplex bDNA assay (Chiron Diagnostics Corp, Walpole, MA) at screening. Patients had compensated liver function with total serum bilirubin ≤2.5 mg/dL (42.75 µmol/L); PTT not >3 s longer than the normal control or INR ≤1.5; serum albumin ≥3.0 g/dL; no history of variceal bleeding, ascites requiring diuretics or paracentesis, or encephalopathy. Patients were required to have evidence of CHB upon liver biopsy performed at screening or within 1 year prior to randomisation and following incomplete response to lamivudine[62].		HBV DNA by PCR log_{10} copies/mL, mean (±SD)		9.48 (1.81)	9.24 (1.56)
			ALT (U/L), mean (±SD)		123.9 (109.72)	131.9 (165.11)
			Viral genotype n (%)	A	37 (26)	32 (22)
				B	23 (16)	1 (12)
				C	27 (19)	28 (19)
				D	45 (32)	56 (39)
				F	4 (3)	3 (2)
				other, indeterminate or missing	5 (4)	9 (6)
014[64]	Eligible patients were men and women aged >16 years with CHB infection who were considered to be lamivudine refractory on the basis of documented viremia after receiving at least 24 weeks of therapy or documented evidence of a lamivudine resistance-associated substitution while receiving lamivudine. Viremia was defined as HBV DNA levels ≥10 pg/mL by the column-based hybridisation assay (Abbott, Abbott Park, IL), ≥25 pg/mL by the chemiluminescent molecular hybridisation assay (Digene, Silver Spring, MD) or ≥10 MEq/mL by the Chiron bDNA assay (Chiron, Emeryville, CA) on two determinations at least 2 weeks apart. Patients were required to have aspartate aminotransferase and ALT levels ≤10×ULN and well-compensated liver function denoted by PTT not >3 s longer than normal (or INR 2.23), serum albumin ≥3.0 g/dL, and total serum bilirubin ≤2.5 mg/dL (42.75 µmol/L)[64].	Patients were excluded if they were coinfected with hepatitis C virus, hepatitis delta virus or HIV; had another form of liver disease or a liver transplant; had received immunomodulator therapy (IFNα, or thymosin-α1) within 24 weeks before randomisation; or had received prior antiviral therapy with NAs other than lamivudine for >4 weeks. Women of childbearing potential were also excluded[64].	**Criteria**[64]		**Entecavir 1 mg N=42**	**Lamivudine 100 mg N=45**
			Age (years), mean (±SD)		48 (13)	48 (15)
			Gender (% male)		39 (93)	34 (76)
			HBeAg-positive, n (%)		27 (64)	32 (71)
			HBV DNA by PCR log10 copies/mL, mean (± SD)		9.07 (1.54)	9.28 (0.82)
			ALT (U/L), mean (± SD)		141 (186)	110 (97)
			Viral genotype n (%)	A	13(31)	18(40)
				B	5(12)	5(11)
				C	8(19)	8(18)
				D	14(33)	14(31)
				Other	2(4)	0(0)

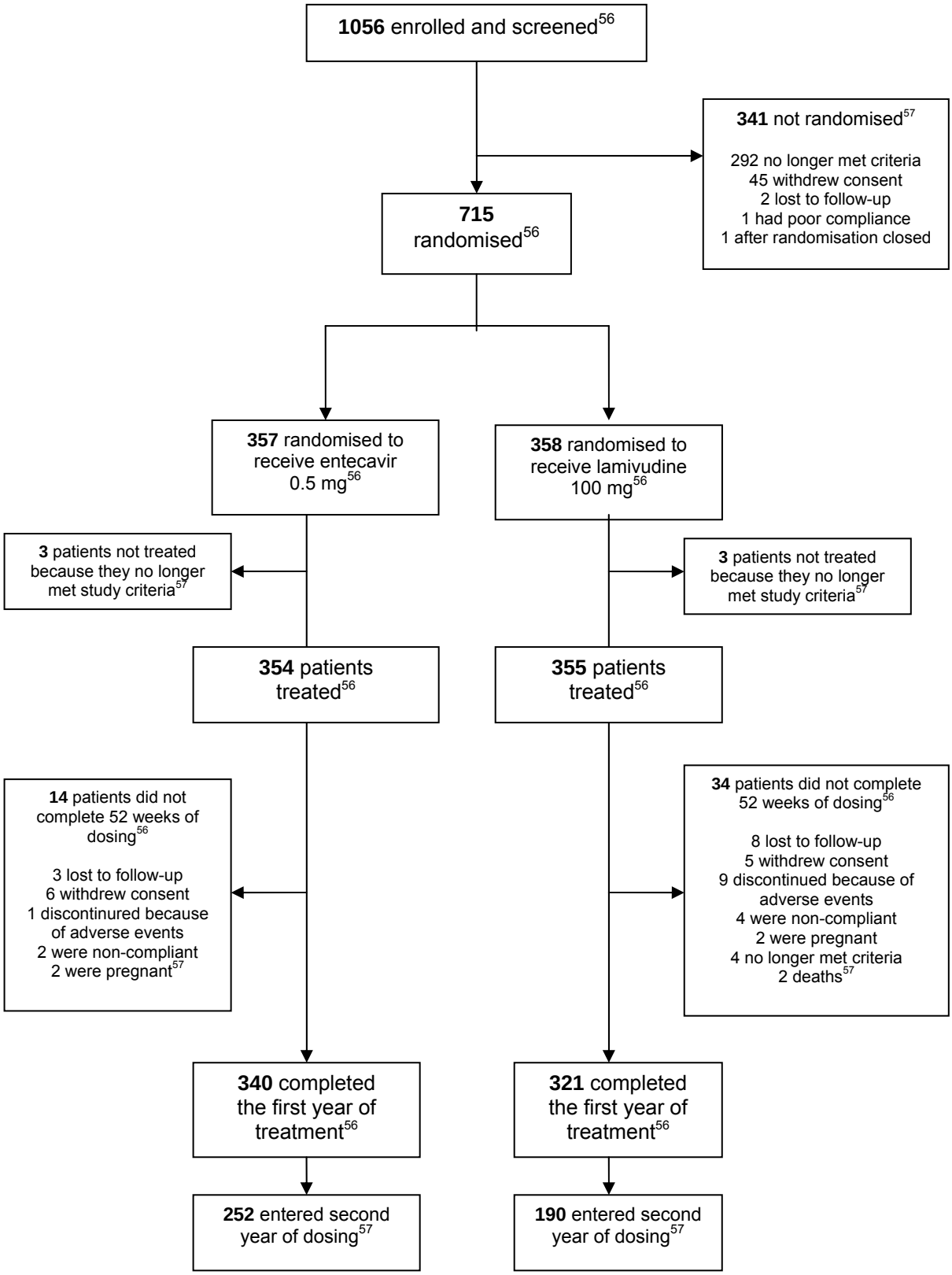
AFP: alpha fetoprotein; ALT: alanine aminotransferase; bDNA: branched-chain DNA; CSR: clinical study report; HBsAg: hepatitis B surface antigen; IFN: interferon; INR: international normalised ratio; NA: nucleo(s/t)ide analogue; PCR: polymerase chain reaction; SD: standard deviation; ULN: upper limit of normal

5.3.3 Patient numbers

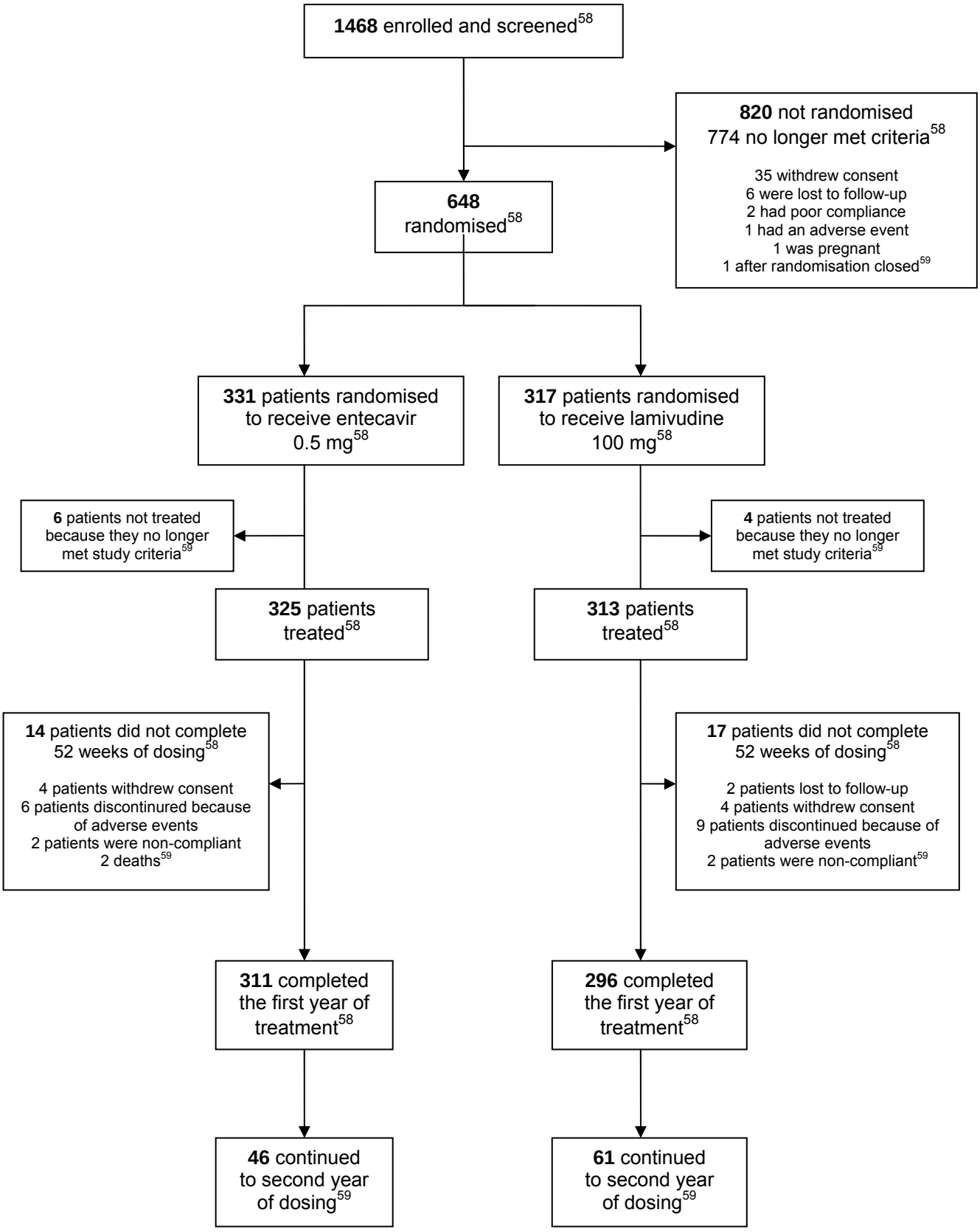
RCT	Number of patients enrolled	Number of patients randomised	Number of patients treated	Patients excluded after treatment commenced	Locations
022[56]	1056 patients enrolled[56]	715 patients were randomised[56]	709 patients were treated with at least one dose of study drug. Among those who started receiving the study drug, 340 patients assigned to the entecavir group (95%) and 321 assigned to the lamivudine group (90%), completed 52 weeks of treatment[56].	14 patients in the 0.5-mg entecavir group and 34 patients in the 100-mg lamivudine group did not complete the first year of dosing[56].	Patients were enrolled at 137 centres worldwide, including Europe (41 centres), North America (40), Asia (26), Australia (12) and South America (18)[56].
027 [58]	1468 patients who were enrolled and screened[58]	648 were randomly assigned to treatment (331 to the entecavir group and 317 to the lamivudine group)[58]	638 patients (325 in the entecavir group and 313 in the lamivudine group) received at least one dose of study drug. 311 patients assigned to the entecavir group and 296 assigned to the lamivudine group completed 52 weeks of treatment[58].	No patient discontinued treatment because of treatment failure or lack of efficacy during the 52-week, blinded treatment period[58].	Patients were enrolled at 146 centers worldwide, including Europe (Italy, Hungary, Czech Republic, Slovakia, Greece, Poland, Italy, Turkey, Portugal, Netherlands, UK, Denmark, Switzerland, Germany, Belgium, Spain) and the Middle East (Israel), Asia (Hong Kong,Taiwan, Malaysia, Indonesia), Australia, North America (USA, Canada), South America (Argentina, Mexico, Peru, Brazil) and Russia[58].
023[60]	962 patients were enrolled[60]	525 patients were randomised[60]	519 patients received their assigned study medication (entecavir 258, lamivudine 261). 499 (entecavir 251, lamivudine 248) completed the first year of dosing. 193 patients and 146 patients in the entecavir 0.5 mg and lamivudine 100 mg groups continued blinded treatement in the second year of the study. 50 patients and 41 patients in the entecavir 0.5 mg and lamivudine 100 mg groups discontinued study drug and were followed up for 24 weeks off treatment[60].	20 patients discontinued from the study during the first year of treatment (7 and 13 in the entecavir 0.5 mg and lamivudine 100 mg groups, respectively)[60].	Patients were enrolled in 26 study centres in China[60].

026 [62]	420 patients were enrolled and screened[62]	293 were randomsed[62]	286 patients received at least one dose of blinded study drug (entecavir 141, lamivudine 145 patients)[62].	88% of randomised patients completed the first year of dosing. During the first year, fewer patients in the entecavir group (1%) than in the lamivudine group (5%) discontinued treatment because of adverse events. Five lamivudine-treated patients (3%) and two entecavir-treated patients (1%) withdrew consent during the first year[62].	Patients were enrolled at 84 sites in North America (28), South America (5), Europe and the Middle East (28), Australia (6), and Asia (17)[62].
014[64 65]	A total of 259 subjects were enrolled[65].	182 patients randomised[64]	181 patients received at least one dose of blinded study drug (45 patients in the lamivudine arm and 42, 47, and 47 patients in the entecavir 1.0, 0.5 and 0.1 mg arms, respectively). A total of 172 patients (95%) completed 24 weeks of blinded treatment, and 138 (76%) completed 48 weeks of blinded treatment[64].	28 patients (15%), mainly from the lamivudine (14 patients) and entecavir 0.1 mg (11 patients) groups, discontinued blinded treatment because of insufficient virological response between weeks 24 and 48. Seven patients (4%) discontinued blinded treatment because of insufficient virological response at or after week 48. A total of 13 patients discontinued study treatment due to an adverse event or abnormal laboratory finding; these were equally distributed between the treatment groups[64].	Patients were enrolled at 41 study centers in 14 countries (Australia, Canada, France, Greece, Italy, Malaysia, The Netherlands, Pakistan, the Philippines, Poland, Singapore, Spain, Taiwan, and the United States)[64].

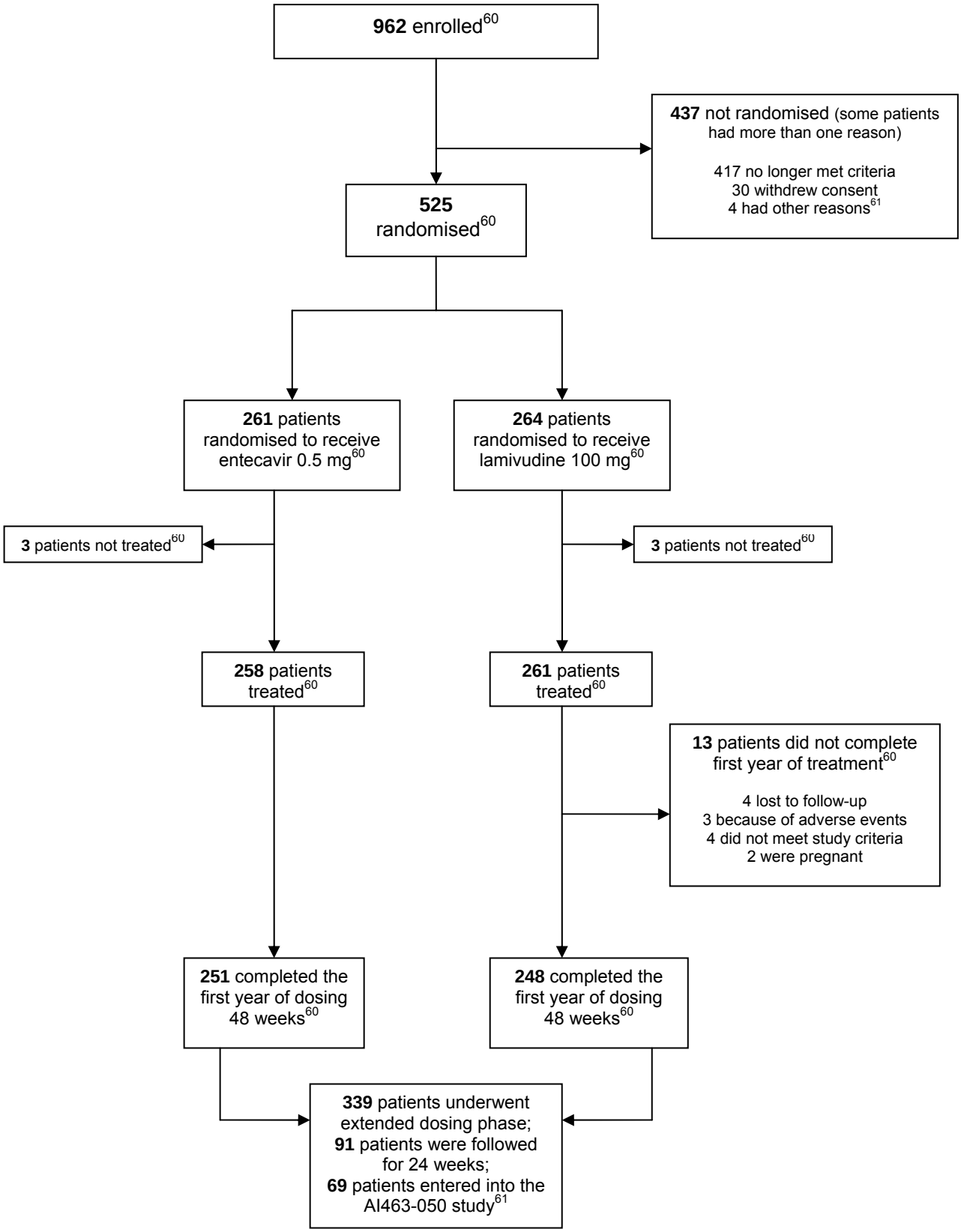
5.3.3.1 CONSORT flow chart: 022 RCT



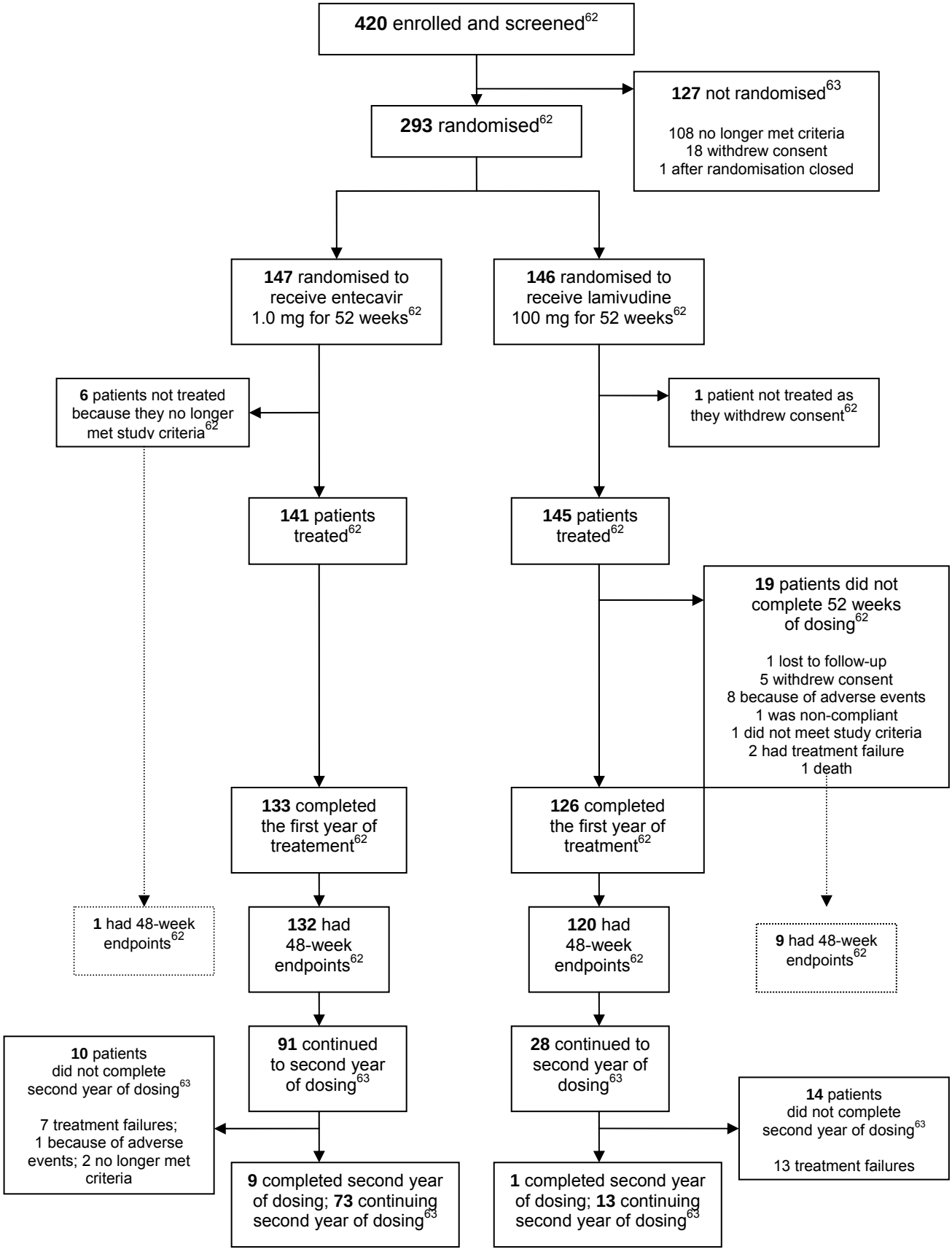
5.3.3.2 CONSORT flow chart: 027 RCT



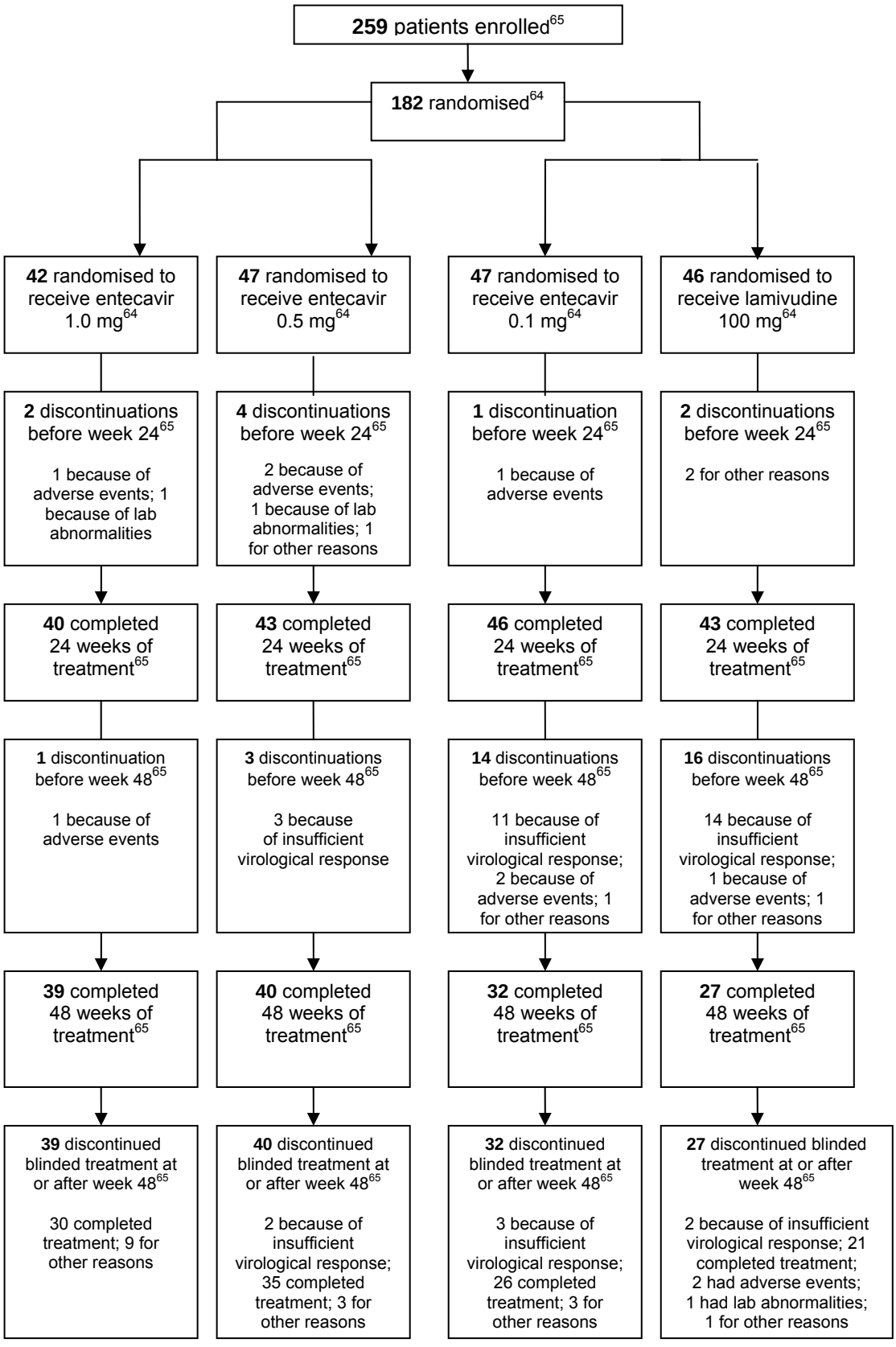
5.3.3.3 CONSORT flow chart: 023 RCT



5.3.3.4 CONSORT flow chart: 026 RCT



5.3.3.5 CONSORT flow chart: 014 RCT



5.3.4 Outcomes

RCT	Primary outcomes and measures	Secondary outcomes and measures	Validity of outcome and measures
022[56] [1]	The primary efficacy endpoint was the proportion of patients with histological improvement, defined as improvement by at least 2 points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline[56].	Secondary efficacy endpoints at week 48 included[56]: • reduction in HBV DNA level from baseline • proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (version 2.0; LLOQ, 300 copies/mL); • decrease in the Ishak fibrosis score; • HBeAg loss; HBeAg seroconversion (HBeAg loss and the appearance of HBe antibody); • normalistion of serum ALT. <u>Second year cohort – proportion of patients with:</u> HBV DNA <300 copies/mL, ALT normalisation ≤1×ULN, HbeAg seroconversion[1] Cumulative confirmed analysis (cumulative probability of achieving a confirmed endpoint – defined as two sequestional measurements or last on treatment measurement meeting the success criteria – does not imply maintenance of response)[1] Safety analysis	Histological analysis and fibrosis are reported as the most consistently predictive with regard to disease progression. The 2-point change in Knodell score with no worsening of fibrosis is now commonly used as an endpoint. The 2006 EMEA CHMP guidance notes for analysis of large patient groups states that this change is acceptable as an endpoint. Study secondary endpoints which are clinically valid and currently recommended by external agencies include single and composite measures from HbeAg seroconversion, number HBV viral load "undetectable", viral load (HBV DNA measured by PCR) and ALT normalisation endpoints.
027 [58] [1]	The primary efficacy endpoint was the proportion of patients with histologic improvement, defined as improvement by at least 2 points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score at week 48, relative to baseline[58].	Secondary efficacy endpoints at week 48 included[58]: • reduction in HBV DNA level from baseline • proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (version 2.0; LLOQ, 300 copies/mL); • decrease in the Ishak fibrosis score; • normalistion of serum ALT (<1.0×ULN) <u>Second year cohort – proportion of patients with:</u> HBV DNA <300 copies/mL, ALT normalisation ≤1xULN, HbeAg seroconversion[1] Cumulative confirmed analysis (cumulative probability of achieving a confirmed endpoint – defined as two sequestional measurements or last	Histological analysis and fibrosis are reported as the most consistently predictive with regard to disease progression. The 2-point change in Knodell score with no worsening of fibrosis is now commonly used as an endpoint. The 2006 EMEA CHMP guidance notes for analysis of large patient groups states that this change is acceptable as an endpoint. Study secondary endpoints which are clinically valid and currently recommended by external agencies include single and composite measures from HbeAg seroconversion, number HBV viral load "undetectable", viral load (HBV DNA measured by PCR) and ALT normalisation endpoints.

		on treatment measurement meeting the success criteria – does not imply maintenance of response) [1] Safety analysis	
023[60]	The primary objective was to determine the proportion of subjects in each treatment group (entecavir versus lamivudine) who achieved a response for the composite endpoint: HBV DNA <0.7 MEq/mL by bDNA assay and serum ALT <1.25×ULN at week 48[60].	Secondary efficacy endpoints included the mean reduction from baseline in HBV DNA by PCR assay (Roche Cobas Amplicor HBV Monitor version 2, LLOQ 300 copies/mL) at week 48; and the proportions of patients who achieved each of the following endpoints at week 48: HBV DNA <300 copies/mL (by PCR assay), HBeAg loss, HBeAg seroconversion (HBeAg loss/HBeAb gain), and ALT normalisation (ALT ≤1×ULN)[60]. Safety analysis	Reduction in HBV DNA, seroconversion of HbeAg, histological improvement and biochemical improvement are all recognised measure of outcome which represent a true clinical outcome.
026[62]	The two co-primary efficacy endpoints were histological improvement, defined as a 2-point decrease in the Knodell necroinflammatory score, and no worsening of the Knodell fibrosis score on the week 48 liver biopsy specimen compared with baseline; and achievement of the composite end point, defined as serum HBV DNA <0.7 MEq/mL by bDNA assay and ALT <1.25×ULN at week 48[62].	Secondary efficacy endpoints included[62]: • the proportion of patients with HBV DNA <300 copies/mL by PCR assay; • the mean $\log_{10}$ change from baseline in serum HBV DNA; • decrease of ≥1 point in the Ishak fibrosis score; • rates of HBeAg loss and seroconversion (loss of HBeAg and appearance of anti-HBe); • normalisation of serum ALT (defined per protocol as <1.25×ULN and subsequently reanalysed using the more stringent definition of ALT ≤1.0×ULN.) Among responders, sustained response was defined as persistence of HBV DNA <0.7 MEq/mL and HBeAg-negative at week 24 of treatment[62]. Safety analysis	Histological analysis and fibrosis are reported as the most consistently predictive with regard to disease progression. The 2-point change in Knodell score with no worsening of fibrosis is now commonly used as an endpoint. The 2006 EMEA CHMP guidance notes for analysis of large patient groups states that this change is acceptable as an endpoint. Study secondary endpoints which are clinically valid and currently recommended by external agencies include single and composite measures from HbeAg seroconversion, number HBV viral load "undetectable", viral load (HBV DNA measured by PCR) and ALT normalisation endpoints.
014[64]	The primary objective was to determine the proportion of subjects in each treatment group who achieved undetectable HBV DNA levels as measure by bDNA assay at week 24. (LLOQ 0.7 MEq/mL [700,000 copies/mL])[64]	Secondary efficacy endpoints included[64]: • proportion of subjects who achieve undetectable HBV DNA by bDNA assay at week 48; • proportion of subjects who achieve undetectable HBV DNA by PCR assay at weeks 24 and 48; • mean reduction in $\log_{10}$ HBV DNA levels by	Reduction in HBV DNA, seroconversion of HbeAg, histological improvement and biochemical improvement are all recognised measure of outcome which represent a true clinical outcome.

		PCR assay at week 24; • proportion of subjects who were positive for HBeAg at baseline who have loss of HBeAg at week 48; • proportion of subjects who were positive for HBeAg at baseline who achieve seroconversion at week 48; • proportion of subjects who had abnormal ALT at baseline who achieve normalisation of ALT at weeks 24 and 48. Safety analysis	

ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHMP: Committee for Human Medicinal Products; EMEA: European Agency for the Evaluation of Medicinal Products; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; LLOQ: lower limit of quantification; PCR: polymerase chain reaction; ULN: upper limit of normal.

5.3.5 Statistical analysis and definition of study group

Hypotheses, objectives	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 022[56] [57]			
The study hypothesis was that entecavir 0.5 mg qd would have clinical efficacy (as measured by improvement in liver histology) that was noninferior (similar) to and potentially superior to lamivudine 100 mg qd in adults with CHB infection who were HBeAg-positive[1].	A two-stage evaluation was planned. First, noninferiority to lamivudine was tested, and if noninferiority was established, a second test for superiority was conducted. The study had a single primary endpoint (histological improvement). Patients with missing or inadequate biopsy specimens obtained at week 48 were considered not to have had a histological response. In analyses of HBV DNA values, HBV serological data and ALT levels, treated patients with a missing value for an endpoint were considered not to have had a response for that endpoint. To compare the means of continuous variables t-tests were used based on linear regression models, adjusted for baseline measurements. There were no interim analyses of efficacy. All reported p-values are two-sided and were not adjusted for multiple testing[56].	With 315 subjects per group, there is 90% power to demonstrate noninferiority for the difference in proportion of subjects with histological improvement assuming[56]: • a response rate of 60% for lamivudine and ≥64% for entecavir subjects with baseline and week 48 biopsy pairs; • a 25% rate of missing week 48 biopsies, which are regarded as failures for the purpose of sample size calculation, with missing status independent of the potential biopsy results.	The principal testing methodology was based on the modified ITT method, in which subjects with missing measurements at week 48 were counted as failures (NC=F method). The ITT efficacy dataset includes data collected on treated subjects who are defined as randomised subjects treated with at least one dose of study therapy: entecavir or lamivudine[57].
Study 027[58] [59]			
The current study was designed to compare the efficacy and safety of entecavir with that of lamivudine after 48 weeks of treatment in patients with HBeAg-negative CHB who had not previously received a nucleoside analogue[1].	A two-stage evaluation was planned. First, noninferiority to lamivudine was tested, and if noninferioritywas established, a second test for superiority was conducted. The study had a single primary endpoint (histological improvement). To compare the means of continuous variables, t-tests were used based on linear regression models, adjusted for baseline measurements. There were no interim analyses of efficacy. All reported p-values are two-sided and were not adjusted for multiple testing[58].	The planned sample size – 315 per group – had 90% power to demonstrate noninferiority with respect to the primary efficacy endpoint, assuming response rates of 60% for lamivudine and 64% for entecavir, a 25% rate of missing biopsy specimens obtained at week 48, and a −10% boundary for the 95% lower confidence limit for the difference in proportions[58].	Patients with missing or inadequate biopsy specimens obtained at week 48 were considered not to have had a histological response. In proportion, analyses of HBV DNA levels and ALT levels, treated patients with a missing value for an endpoint were considered not to have had a response for that endpoint[59].

Study 023[60 61]			
The hypothesis of this study was that entecavir 0.5 mg qd has clinical efficacy (as measured by undetectable HBV DNA levels by the bDNA assay [<0.7 MEq/mL] and normalisation of ALT [<1.25×ULN]) at week 48 that is similar (noninferior) and potentially superior to lamivudine 100 mg qd in adults with CHB infection who are either HBeAg-positive or -negative and HBeAb-positive at baseline[1].	For the analysis of the primary endpoint, a two-stage evaluation was planned. In the first stage, noninferiority of entecavir to lamiduvine is established if the lower limit of the two-sided 95% confidence interval for the difference in proportions of subjects achieving a response on the composite endpoint is greater than –10%. Provided noninferiority is demonstrated, a second-stage test for superiority is conducted. Analyses of efficacy endpoints focus on treated subjects and are based on the ITT dataset. Treatment comparisons for binary variables are stratified by baseline HBeAg with Cochran–Mantel–Haenszel weights. Confidence intervals for difference estimates are based on the normal approximation to the binomial distribution. Comparisons of continuous variables use t-tests based on linear regression models with covariates for baseline measurement, baseline HBeAg status (positive or negative) and treatment group. P-values are based on two-sided tests[60].	The target sample size of 225 subjects per treatment group provided 90% power to demonstrate superiority assuming response rates of 55% for entecavir[60] and 40% for lamivudine for subjects who are HBeAg-positive at baseline and response rates of 75% for entecavir and 60% for lamivudine for subjects who are HbeAg-negative at baseline[61].	Analyses of efficacy endpoints focus on treated subjects and are based on the ITT data set. In the principal analysis of binary endpoints, subjects with missing week 48 measurements are treated as having a nonrepsonse for that endpoint[61].
Study 026[62 63]			
The study hypothesis is that switching to entecavir 1.0 mg qd will be superior (as measured by improvement of liver histology and/or reducing HBV DNA to undetectable level by the branched DNA assay and in normalisation of ALT) to continued therapy with lamivudine 100 mg qd in adults with CHB infection who are HBeAg-positive and have an incomplete response (were refractory) to current lamivudine therapy[1].	The cohort included all randomised patients who received at least one dose of study medication (modified ITT method), and patients with missing measurements at week 48 were counted as failures (non-completer failure). The two co-primary endpoints – histological improvement and the composite endpoint – were evaluated separately for each subject. A Bonferroni adjustment was applied for testing superiority with an overall 2-sided significance level of 5%. Comparisons of the means of continuous parameters used t-tests based on linear regression models, adjusted for baseline measurements. Mean differences were based on patients with both baseline and week 48 measurements. Binary variables were summarised by counts and proportions. Confidence intervals for differences in proportions were based on the normal approximation to the binomial distribution[62].	For histological improvement, the planned sample size of 135 patients per group provided 90% power to detect superiority of entecavir to lamivudine, assuming a response rate of 25% for lamivudine and ≥50% for entecavir; a 25% rate of missing data; and a 2-sided significance level of 2.5%. For the composite endpoint, the planned sample size of 135 patients per group provided 90% power to detect superiority of entecavir to lamivudine, assuming a response rate of 15% for lamivudine and ≥35% for entecavir; a 5% rate of subjects missing the week 48 composite endpoint with missing status independent of potential HBV DNA results; and a 2-sided significance level of 2.5%[62].	The principal testing methodology is based on a modified ITT method in which subjects with missing measurements at week 48 are counted as failures (NC=F method)[63].

Study 014[64 65]			
Designed to assess the efficacy and safety of entecavir versus continued lamivudine in patients with CHB infection who remained viremic after at least 24 weeks of lamivudine therapy or had documented lamivudine resistance-associated substitutions. Three different doses of entecavir (1.0, 0.5 and 0.1 mg/day) were evaluated with the aim of selecting an optimal dose for further study in Phase 3 clinical trials in lamivudine-refractory patients[65].	Data on efficacy and safety were analysed for all randomised patients who received one or more doses of study medication. For the primary efficacy analysis, the difference between treatment groups in proportions of patients with undetectable HBV DNA levels, the 98.3% confidence intervals, and the p-values were computed using a normal approximation to the binomial distribution. A dose of entecavir was determined to be superior to lamivudine if the p-value was <0.0167 (an overall 0.05 2-sided significance level adjusted for three comparisons). Other binary endpoints were assessed similarly with 95% confidence intervals; entecavir was determined to be superior to lamivudine if the p-value was ≤0.05 Comparisons of the means of continuous parameters were performed using t-tests based on linear regression adjustment for baseline HBV DNA levels. Mean differences were based on patients who completed dosing[64].	The planned sample size of 45 patients per group had 90% power to demonstrate superiority of a dose of entecavir compared with lamivudine for the primary end point (HBV DNA <0.7 MEq/mL by bDNA assay at week 24) with a 2-sided significance level of 0.05 adjusted for multiple comparisons, assuming a 20% success rate for lamivudine and a 60% success rate for the entecavir dose. This sample size would also provide 90% power to demonstrate a ≥1.0 $\log_{10}$ difference between doses of entecavir in mean HBV DNA levels measured at week 24 using the PCR assay (assuming a within-group standard deviation of ≥1.25 $\log_{10}$ in these measurements and a 2-sided significance level of 0.05) [64].	Patients who discontinued treatement or had missing data were regarded as having failed to respond to therapy[65].

ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ITT: intention to treat; PCR: polymerase chain reaction.

5.3.6 Critical appraisal of relevant RCTs

Study	Critical appraisal
	Question 1: How was allocation concealed?
014	Double-blind
022	Double-blind
023	Double-blind
026	Double-blind
027	Double-blind

Study	Critical appraisal
	Question 2: Which randomisation technique was used?
014	Randomisation was performed using a centralised interactive voice randomization system and was stratified by site
022	Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each centre.
023	Investigative staff called the Randomisation Centre, and a subject number was randomly assigned by an interactive voice recognition system. A randomised block design stratified by site and by HBeAg status was used.
026	Eligible patients were randomised centrally using an interactive voice response system. Randomisation was accomplished using blocks of permuted treatment assignments and was stratified by study site.
027	Investigative staff called the Randomisation Centre, and a subject number or patient identification number was assigned. A randomised block design stratified by site was used.

Study	Critical appraisal
	Question 3: Was follow-up adequate?
014	At least 76 weeks with up to 96 weeks for partial responders
022	At least 76 weeks with up to 120 weeks for nonresponders
023	At least 76 weeks with up to 96 weeks for partial responders or relapses
026	At least 76 weeks with up to 120 weeks for partial responders
027	At least 76 weeks with up to 120 weeks for partial responders

Study	Critical appraisal
	Question 4: Were individuals undertaking the outcomes assessments aware of allocation?
014	No
022	No
023	No
026	No
027	No

Study	Critical appraisal
	Question 5: Was a justification of the sample size provided?
014	Yes, the planned sample size was calculated to have a 90% power to show superiority of a dose of entecavir compared with lamivudine for achieving the primary endpoint. This would also have a 90% power of showing a 1.0 $\log_{10}$ difference in HBV DNA (secondary outcome).
022	Yes, the planned sample size had 90% power to demonstrate noninferiority with respect to the primary efficacy endpoint.
023	Yes, the planned sample size had a 90% power to demonstrate noninferiority assuming a conservative entecavir efficacy estimate and a 90% power to demonstrate superiority assuming the expected efficacy.
026	Yes, the planned sample size had a 90% power to detect superiority of a dose of entecavir compared with lamivudine for achieving the co-primary outcomes.
027	Yes, the planned sample size had a 90% power to demonstrate noninferiority with respect to the primary outcome.

Study	Critical appraisal
	Question 6: Was the design parallel or crossover? Is there risk, for crossover designs, of carry-over effect?
014	Parallel
022	Parallel
023	Parallel
026	Parallel
027	Parallel

Study	Critical appraisal
	Question 7: Was the RCT conducted in the UK?
014	RCT was multinational, with patients from Australia, Canada, France, Greece, Italy, Malaysia, The Netherlands, Pakistan, the Philippines, Poland, Singapore, Spain, Taiwan, and the USA, though not in the UK.
022	RCT was multinational with participating centres from Asia, Australasia, Europe, North America and South America. A proportion of the sample was from the UK.
023	No, all sites were in China.
026	RCT was multinational with participating centres from Asia, Australasia, Europe, North America and South America. None of the sample was from the UK.
027	RCT was multinational with participating centres from Asia, Australasia, Europe, North America and South America. A proportion of the sample was from the UK.

Study	Critical appraisal
	Question 8: How patients included in the RCT compare with patients likely to receive the intervention in the UK?
014	Comparable, CHB patients with compensated liver disease and either HBeAg-positive or -negative. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.
022	Comparable, CHB patients with compensated liver disease and HBeAg-positive. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.
023	Comparable, CHB patients with compensated liver disease and either HBeAg-positive or -negative. As UK patients with CHB are often immigrants of whom some are of Chinese origin, the patient population is of some relevance to the UK.
026	Comparable, CHB patients with compensated liver disease and HBeAg-positive. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.
027	Comparable, CHB patients with compensated liver disease and HBeAg-negative. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.

Study	Critical appraisal
	Question 9: Are dosage regimens within those cited in the SmPC?
014	Entecavir studied at a range of 0.1–1.0 mg/day, which includes those doses cited within the SmPC. The lamivudine dose was according to the SmPC.
022	Yes
023	Yes
026	Yes
027	Yes

Study	Critical appraisal
	Question 10: Were study groups comparable?
014	Yes, stated as similar
022	Yes, balanced
023	Yes, balanced
026	Yes, balanced
027	Yes, balanced

Study	Critical appraisal
	Question 11: Were the statistical analyses performed appropriate?
014	Efficacy analysis based on all randomised patients who received one or more doses of study medication. Binary variables were compared using the chi-squared test with 1 degree of freedom. Comparisons of the means of continuous parameters were performed using t-tests based on linear regression models. Kaplan–Meier estimators were used for time-to-event analyses.
022	Efficacy analysis based on all randomised patients who received one or more doses of study medication. Binary variables were compared using the chi-squared test with 1 degree of freedom. Continuous variables were compared using t-tests based on linear regression models. Kaplan–Meier estimators were used for time-to-event analyses.
023	Efficacy analysis based on a modified intention-to-treat population. Binary variables assessed using Cochran–Mantel–Haenszel weights to stratify differences. Continuous variables were compared using t-tests based on linear regression models. Kaplan–Meier estimators were used for time-to-event analyses.
026	Efficacy analysis based on all randomised patients who received one or more doses of study medication. A Bonferroni adjustment was applied for testing superiority amongst binary co-primary endpoints. Comparisons of the means of secondary continuous parameters used t-tests based on linear regression models. Kaplan–Meier estimators were used for time-to-event analyses.
027	Efficacy analysis based on all randomised patients who received one or more doses of study medication. Binary variables were compared using the chi-squared test with 1 degree of freedom. Comparisons of continuous variables used t-tests based on linear regression models. Kaplan–Meier estimators were used for time-to-event analyses.

5.4 Results of the relevant comparative RCTs

Summary data on the results of the relevant RCTs selected in the systematic review are presented in this section. This includes results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem, i.e.:

- HBeAg/HBsAg seroconversion rate
- virological response (HBV DNA)
- histological improvement (inflammation and fibrosis)
- biochemical response (e.g. ALT levels)
- development of viral resistance.

Full details of all outcome measures are also presented in tabular form.

Results of relevant RCTs are presented as follows:

- Section 5.4.1: Entecavir versus lamivudine in NA-naïve HBeAg-positive CHB patients (Study 022)
- Section 5.4.2: Entecavir versus lamivudine in NA-naïve HBeAg-negative CHB patients (Study 027)
- Section 5.4.3: Entecavir versus lamivudine in NA-naïve HBeAg-positive/-negative CHB patients (Study 023)
- Section 5.4.4: Entecavir versus lamivudine in lamivudine-refractory CHB patients (Study 026, Study 014)

Data come primarily from the publication for each study. Where further detail was required, this has been obtained from the clinical study report, and this is specifically indicated and referenced. All references (see Section 0), including extracts from clinical study reports, are provided with this submission

5.4.1 Entecavir versus lamivudine in NA-naïve, HBeAg-positive CHB patients

022: A Phase 3 sudy of the safety and antiviral activity of entecavir versus lamivudine in adults with chronic hepatitis B infection who are positive for HBeAg[56 57]

Results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem are presented below. Detailed results are presented in Table 5.5.

Primary outcome

The primary efficacy endpoint was the proportion of patients with histological improvement, defined as improvement by at least 2 points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline.

Primary outcome: Histological improvement at week 48**:** ≥2 point decrease in the Knodell necroinflammatory score with no worsening of fibrosis (≥1 point increase in Knodell fibrosis score) relative to baseline at week 48.

Results: At week 48, 0.5 mg entecavir was superior to lamivudine in histological improvement in HBeAg-positive patients[56]

	Entecavir 0.5 mg (N=354)	Lamivudine 100 mg (N=355)	p-value
n (%)	226/314 (72)	195/314 (62)	0.009

Key secondary outcomes

The secondary efficacy endpoints of the study at week 48 included; the reduction in HBV DNA level from baseline, the proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (300 copies/mL); the decrease in the Ishak fibrosis score; HBeAg loss; HBeAg seroconversion (HBeAg loss and the appearance of HBe antibody); normalisation of serum ALT.

Additional assessments included: 24-week post-treatment responses, 2-year responses in virological-only responders at week 48, and 2-year cumulative confirmed responses.

Key secondary outcomes: At week 48: HBV DNA <300 copies/mL by PCR (virological response), ALT ≤1.0×ULN (biochemical response), HBeAg seroconversion and development of viral resistance.

Results: At week 48: 0.5 mg entecavir was superior to lamivudine in both virological and biochemical responses in HBeAg-positive patients[56].

	Entecavir 0.5 mg	**Lamivudine 100 mg**	**p-value**
Virological response, n (%)	236/354 (67)	129/355 (36)	<0.001
Biochemical response, n (%)	242/354 (68)	213/355 (60)	0.02
HBeAg seroconversion, n (%)[56]	74/354 (21)	64/355 (18)	0.33

Responses through to 2 years [1]

- 81% (197/243) of entecavir-treated NA-naïve, HBeAg-positive CHB patients who continue into the second year of treatment achieved undetectable HBV DNA (<300 copies/mL) by the end of dosing [1].
- 79% (193/243) of entecavir-treated NA-naïve, HBeAg-positive CHB patients who continue into the second year of treatment achieved ALT normalisation by the end of dosing[1].
- Treatment of NA-naïve, HBeAg-positive CHB patients with 0.5 mg/day of entecavir for up to 96 weeks (n=354) results in cumulative responses rates of 80% for HBV DNA <300 copies/mL by PCR, 87% for ALT normalisation and 31% for HbeAg seroconversion [1].

Table 5.5: Study 022 – Summary of results[56 57 1]

Study design[56]	Population[56]	Endpoints	Results			
			Entecavir 0.5 mg (N=354)	Lamivudine 100 mg (N=355)	Difference entecavir – lamivudine (95% CI)	p-value
Randomised, double-blind, active comparator Entecavir 0.5 mg qd versus lamivudine 100 mg qd 52 weeks (with 24-week follow-up post-treatment) Continued blinded treatment for an additional 44 weeks in partial responders (total 96 weeks' dosing)	NA-naïve, HBeAg-positive CHB patients	**Week 48**[56]				
		Primary endpoint: histological improvement, n (%)	**226/314 (72)**	**195/314 (62)**	**9.9 (2.6, 17.2)**	**0.009**
		Ishak fibrosis score improvement, n (%)	121/314 (39)	111/314 (35)	3.2 (–4.4, 10.7)	0.41
		HBV DNA <300 copies/mL by PCR, n (%)	236/354 (67)	129/355 (36)	30.3 (23.3, 37.3)	<0.001
		Mean change HBV DNA by PCR from baseline (log_{10} copies/mL)	–6.9 ± 2	–5.4 ± 2.6	–1.52(-1.78,-1.27)	<0.001
		HBV DNA <0.7 MEq/mL by bDNA, n (%)	322/354 (91)	232/355 (65)	25.6 (19.8, 31.4)	<0.001
		ALT ≤1.0×ULN, n (%)	242/354 (68)	213/355 (60)	8.4 (1.3, 15.4)	0.020
		Loss of HBeAg, n (%)	78/354 (22)	70/355 (20)	2.3 (–3.7, 8.3)	0.45
		HBeAg seroconversion, n (%)	74/354 (21)	64/355 (18)	2.9 (–2.9, 8.7)	0.33
		Complete virological responders: HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN, n (%)	74/354 (21)	67/ 355 (19)		
		Partial response: HBV DNA < 0.7 MEq/mL by bDNA without HBeAg loss, n (%)	247/354 (70)	165/355 (46)		
		Nonresponders: HBV DNA >0.7 MEq/mL by bDNA	19/354 (5)	94/355 (26)		
		24 week post-treatment follow-up for complete virological responders at week 48:[56]	n=74	n=67		
		Sustained HBV DNA <0.7 MEq/mL by bDNA and loss of HBeAg, n (%)	61/74 (82)	49/67 (73)		
		Year 2 cohort, EOD, in virological-only responders:[1,] [redacted]	n=243	n=164		
		HBV DNA <300 copies/mL by PCR at EOD (%)[1]	197/243 (81)	64/164 (39)		
		[redacted]	[redacted]	[redacted]		
		ALT ≤1.0×ULN (%)[1]	193/243 (79)	112/164 (68)		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		

		Cumulative confirmed endpoints* at week 96 (all treated patients):[1] [redacted]	n=354	n=355		
		HBV DNA <300 copies/mL by PCR[1] (%)	284/354 (80)	137/355 (39)		[redacted]
		ALT ≤1.0×ULN[1] (%)	307/354 (87)	280/355 (79)		[redacted]
		[redacted]	[redacted]	[redacted]		[redacted]
		HBeAg seroconversion, n (%)[1] [redacted]	108/354 (31) [1], [redacted]	[redacted]		[redacted]
		HbsAg loss %[1]	5	3		

*Cumulative proportion of treated patients who ever achieved a confirmed endpoint on-treatment; a confirmed endpoint is when 2 sequential measurements meet the success criteria (or last observation).
ALT: alanine aminotransferase; bDNA: branched-chain DNA; CI: confidence interval; EOD: end of dosing; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; qd: once daily; ULN: upper limit of normal.

5.4.2 Entecavir versus lamivudine in NA-naïve, HBeAg-negative CHB patients

027: A Phase 3 study of the safety and antiviral activity of entecavir versus lamivudine in adults with chronic hepatitis B infection who are negative for HBeAg[58 59]

Results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem are presented below. Detailed results are presented in Table 5.6.

Primary outcome

The primary efficacy endpoint was the proportion of patients with histological improvement, defined as improvement by at least 2 points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline.

Primary outcome: Histological improvement at week 48: ≥2 point decrease in the Knodell necroinflammatory score with no worsening of fibrosis (≥1 point increase in Knodell fibrosis score) relative to baseline at week 48.

Results: At week 48, 0.5 mg entecavir was superior to lamivudine in histological improvement in HBeAg-negative patients[58]

	Entecavir 0.5 mg (N=325)	Lamivudine 100 mg (N=313)	p-value
n (%)	208/296 (70)	174/287 (61)	0.01

Key secondary outcomes

The secondary efficacy endpoints of the study at week 48 included: the reduction in HBV DNA level from baseline, the proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (version 2.0; lower limit of quantification 300 copies/mL); the decrease in the Ishak fibrosis score; HBeAg loss; HBeAg seroconversion (HBeAg loss and the appearance of HBe antibody); normalisation of serum ALT.

Additional assessments included: 24-week post-treatment responses, 2-year responses in virological-only responders at week 48, and 2-year cumulative confirmed responses.

Key secondary outcomes: At week 48: HBV DNA <300 copies/mL by PCR (virological response), ALT ≤1.0×ULN (biochemical response), HBeAg seroconversion and development of viral resistance.

Results: At week 48, 0.5 mg entecavir was superior to lamivudine in both virological and biochemical responses in HBeAg-negative patients[58].

	Entecavir 0.5 mg (N=325)	**Lamivudine 100 mg (N=313)**	**p-value**
Virological response, n (%)	293 (90)	225 (72)	<0.001
Biochemical response, n (%)	253(78)	222(71)	0.045
Combined virological and biochemical response, HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN, n (%)[58]	275 (85)	245(78)	0.04

Responses through to 2 years[1]

- Treatment of NA-naïve, HBeAg-negative CHB patients with 0.5 mg/day of entecavir for up to 96 weeks resulted in cumulative response rates of 94% for HBV DNA <300 copies/mL by PCR, and 89% for ALT normalisation[1]

Table 5.6: Study 027 – Summary of results[58] [1]

Study design[58]	Population[58]	Endpoints	Results			
			Entecavir 0.5 mg	**Lamivudine 100 mg**	**Difference entecavir – lamivudine**	**p-value**
			(N=325)	**(N=313)**	**(95% CI)**	
Multicenter, randomised, double-blind, double-dummy versus lamivudine	648 CHB patients					
	HBeAg-positive or -negative					
146 centres worldwide	Anti-HBeAg-positive	**Week 48:**[58]				
52 weeks with 24-week follow-up	Elevated ALT levels with detectable HBV DNA and compensated liver disease due to CHB	**Primary endpoint: histological improvement, n (%)**	**208/296 (70)**	**174/287 (61)**	**9.6 (2.0, 17.3)**	**0.01**
		Ishak fibrosis score improvement, n (%)	107/296 (36)	109/287 (38)		0.65
		HBV DNA <300 copies/mL by PCR (%)	293 (90)	225 (72)	18.3 (12.3, 24.2)	<0.001
		Mean change HBV DNA by PCR (log_{10} copies/mL)	–5.0	–4.50	–0.43 (–0.6, –0.3)	<0.001
	No more than 12 weeks of prior treatment with NA analogues	HBV DNA <0.7 MEq/mL by bDNA, n (%)	309 (95)	279 (89)	5.9 (1.8, 10.1)	0.005
		ALT ≤1×ULN (%)	253 (78)	222 (71)	6.9 (0.2, 13.7)	0.045
		Complete virological responders: HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN, n (%)	275 (85)	245 (78)	6.4 (0.3, 12.4)	0.04
		Partial virological responders: HBV DNA <0.7 MEq/mL with ALT >1.25×ULN	34 (10)	34 (11)		
	Aged ≥16 years old	Nonresponders: HBV DNA ≥0.7 MEq/mL	3 (<1)	18 (6)		
		24-week post-treatment follow-up for complete virological responders at week 48, at EOD:[58, 1]				
		Sustained HBV DNA <0.7 MEq/mL by bDNA and ALT ≤1.0×ULN, n (%)	131/286 (46)	79/253 (31)		
		Year 2 cohort, EOD, in virological-only responders:[1]	n=26	n=28		
		HBV DNA <300 copies/mL by PCR at EOD (%)	25/26 (96)	18/28 (64)		
		ALT ≤1.0×ULN (%)	7/26 (27)	6/28 (21)		
		Cumulative confirmed endpoints* at week 96 (all treated patients):[1]				
		HBV DNA <300 copies/mL by PCR	304/325 (94)	241/313 (77)		0.0001
		ALT ≤1.0×ULN (%)	289/325 (89)	262/313 (84)		0.05

*Cumulative proportion of treated patients who ever achieved a confirmed endpoint on-treatment; a confirmed endpoint is when 2 sequential measurements meet the success criteria (or last observation).
ALT: alanine aminotransferase; bDNA: branched-chain DNA; CI: confidence interval; EOD: end of dosing; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; qd: once daily; ULN: upper limit of normal.

5.4.3 Entecavir versus lamivudine in NA-naïve, HBeAg-positive and -negative CHB patients

023: A Phase 3 study in China of the safety and antiviral activity of entecavir versus lamivudine in adults with chronic hepatitis B infection[60 61]

Results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem are presented below. Detailed results are presented in Table 5.7.

Primary outcome

The primary efficacy endpoint was to determine the proportion of subjects in each treatment group (entecavir versus lamivudine) who achieved a response for the composite endpoint, which consists of both a virological response (as measured by reduction in HBV DNA to below the limit of detection by bDNA assay) and biochemical response (normalisation of ALT) at week 48.

Primary outcome: Virological and biochemical response at week 48: composite endpoint; HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25xULN

Results: At week 48, entecavir 0.5 mg was superior to lamivudine in achieving viral load reduction and ALT normalisation in HBeAg-positive and -negative patients[60].

	Entecavir 0.5 mg (N=258)		Lamivudine 100 mg (N=261)		p-value
	HBeAg+	HBeAg–	HBeAg+	HBeAg–	
Composite endpoint	199/225 (88)	32/33 (97)	143/221 (65)	31/40 (78)	<0.0001 (overall)

Key secondary outcomes

The secondary efficacy endpoints of the study at week 48 included: the reduction in HBV DNA level from baseline, the proportion of patients with undetectable HBV DNA, as measured by the Roche COBAS Amplicor PCR assay (version 2.0; lower limit of quantification 300 copies/mL); the decrease in the Ishak fibrosis score; HBeAg loss; normalisation of serum ALT; incidence of virological rebound, as defined by ≥1 $\log_{10}$ increase in HBV DNA by PCR assay from nadir on blinded treatment.

Additional assessments included: 24-week post-treatment responses and 2-year responses in virological-only responders at week 48.

Key secondary outcomes: At week 48: HBV DNA <300 copies/mL by PCR (virological response), ALT ≤1.0×ULN (biochemical response), HBeAg seroconversion and development of viral resistance.

Results: At week 48: entecavir 0.5 mg was superior to lamivudine in achieving virological and biochemical responses in HBeAg-positive and -negative patients[60].

	Entecavir 0.5 mg (N=258)		**Lamivudine 100 mg (N=261)**		**p-value**
	HBeAg+ (n=255)	HBeAg– (n=33)	HBeAg+ (n=221)	HBeAg– (n=40)	
Virological response, n (%)	166 (74)	31 (94)	83 (38)	29 (73)	<0.0001 overall
Biochemical response, n (%)	200 (89)	31 (94)	172 (78)	31 (78)	0.0003
HBeAg seroconversion, n (%)[60]	33/225 (15)	–	39/221 (18)	–	>0.05

[redacted]

[redacted]

[redacted]

Table 5.7: Study 023 – Summary of results[60 61]

Study design[60]	**Population**[60]	**Endpoints**	**Results**				
			Entecavir 0.5 mg (N=258)		**Lamivudine 100 mg (N=261)**		**p-value**
Randomised, double-blind, active comparator Entecavir 0.5 mg qd; lamivudine 100 mg qd 52 weeks (with 24-week follow-up post-treatment) Continued blinded treatment for an additional 44 weeks in partial responders (total 96 weeks' dosing)	HBeAg-positive and -negative Chinese CHB patients	**Week 48**:[60]	**HBeAg+ (n=255)**	**HBeAg– (n=33)**	**HBeAg+ (n=221)**	**HBeAg– (n=40)**	
		Primary composite endpoint: HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN, n (%)	**199 (88)**	**32 (97)**	**143 (65)**	**31 (78)**	**<0.0001 overall**
		Mean change in HBV DNA from baseline (log_{10} copies/mL)	–6.00	–5.22	–4.30	–4.50	<0.0001 overall
		HBV DNA < 300 copies/mL by PCR (%)	166 (74)	31 (94)	83 (38)	29 (73)	<0.0001 overall
		ALT <1×ULN (%)	200 (89)	31 (94)	172 (78)	31 (78)	
		Loss of HBeAg, n (%)	41 (18)	–	44 (20)	–	
		HBeAg seroconversion, n (%)	33 (15)	–	39 (18)	–	
		Post-treatment, week 24:[60]					
		Consolidated response at week 48 or EOD during year 2	25/225 (11)	25/33 (76)	16/221 (7)	24/40 (60)	
		Sustained consolidated response at week 24 of off-treatment follow-up, n (%)	29/45 (64)	25/32 (78)	16/30 (53)	14/33 (42)	
		[redacted]					

*Cumulative proportion of treated patients who ever achieved a confirmed endpoint on-treatment; a confirmed endpoint is when 2 sequential measurements meet the success criteria (or last observation).
ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHB: chronic hepatitis B; CSR: clinical study report; EOD: end of dosing; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; qd: once daily; ULN: upper limit of normal.

5.4.4 Entecavir versus lamivudine in lamivudine-refractory CHB patients

026: A Phase 3 study of the comparison of entecavir to lamivudine in chronic hepatitis B subjects with incomplete response to current lamivudine therapy[62 63]

Results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem are presented below. Detailed results are presented in Table 5.8.

Primary outcome

The two co-primary efficacy endpoints were histological improvement, defined as a 2-point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score on the week 48 liver biopsy specimen compared with baseline; and achievement of the composite endpoint, defined as serum HBV DNA <0.7 MEq/mL by bDNA assay and ALT <1.25×ULN at week 48.

Co-primary outcomes: Histological improvement: ≥2-point decrease in the Knodell necroinflammatory score with no worsening of fibrosis (≥1-point increase in Knodell fibrosis score) relative to baseline at week 48 compared with baseline.

Combined virological and biological response: HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN.

Results: At week 48, 1.0 mg entecavir was superior to lamivudine for both co-primary endpoints in lamivudine-refractory patients[62]

	Entecavir 1 mg n=141	Lamivudine 100 mg n=145	p-value
Histological improvement	68/124 (55)	32/116 (28)	<0.0001
Combined virological and biological response	77/141 (55)	6/145 (4)	<0.0001

Key secondary outcomes

The secondary efficacy endpoints of the study at week 48 included: the reduction in HBV DNA level from baseline, the proportion of patients with undetectable HBV DNA, (300 copies/mL); the decrease in the Ishak fibrosis score; HBeAg loss and seroconversion; normalisation of serum ALT; incidence of virological rebound, as defined by ≥1 $\log_{10}$ increase in HBV DNA by PCR assay from nadir on blinded treatment.

Additional assessments included; 24-week post-treatment responses and 2-year responses in virological-only responders at week 48.

Key secondary outcomes: At week 48: HBV DNA <300 copies/mL by PCR (virological response), ALT ≤1.0×ULN (biochemical response), HBeAg seroconversion.

Results: At week 48: 1.0 mg entecavir was superior to lamivudine for both virological and biochemical responses in lamivudine-refractory patients[62].

	Entecavir 0.5 mg	Lamivudine 100 mg	p-value
Virological response, n (%)	27/141 (19)	2/145 (1)	<0.0001
Biochemical response, n (%)	86 (61)	22/145 (15)	<0.0001
HBeAg seroconversion, n (%)[62]	11 (8)	4 (3)	0.06

Responses through to 2 years[1]

- 40% (31/77) of entecavir-treated lamivudine-refractory HBeAg-positive CHB patients who continued into the second year of treatment achieved undetectable HBV DNA levels (<300 copies/mL) by the end of dosing[1].
- 81% (62/77) of entecavir-treated lamivudine-refractory HBeAg-positive CHB patients who continued into the second year of treatment achieved ALT normalisation by the end of dosing[1].
- Treatment of lamivudine-refractory HBeAg-positive CHB patients with entecavir for up to 96 weeks (n=141) results in cumulative response rates of 30% for HBV DNA <300 copies/mL by PCR[1], 85% for ALT normalisation[1] and [redacted]

Table 5.8: Study 026 – Summary of results[62, 63] [1].

Study design[62]	Population[62]	Endpoints	Results			
Multicenter, randomised, double-blind, lamivudine-controlled 84 centres worldwide 52 week (with 24-week follow-up)	286 CHB patients aged ≥16 years that were incomplete responders to lamivudine. Patients were HBsAg-positive with elevated ALT, detectable HBV DNA and compensated liver disease due to CH		**Entecavir 1.0 mg**	**Lamivudine 100 mg**	**Difference (entecavir–lamivudine)**	**p-value**
		Week 48: [62]	N=141	N=145	(95% CI)	
		Co-primary outcome: histological improvement, n (%)	**68/124 (55)**	**32/116 (28)**	**27.3 (13.6, 40.9)[h]**	**<0.0001**
		Co-primary outcome: HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25×ULN, n (%)	**77/141 (55)**	**6/145 (4)**	**50.5 (40.4, 60.6)**	**<0.0001**
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		HBV DNA <300 copies/mL by PCR (%)	27 (19)	2 (1)	(11,24.5)	<0.0001
		Mean change HBV DNA by PCR (log_{10} copies/mL)	–5.1	–0.48	–4.4 (–4.8, –4.0)	<0.0001
		ALT ≤1.0×ULN (%)	86 (61)	22(15)	51.7 (35.9, 55.8)	<0.0001
		Loss of HBeAg, n (%)	14/134 (10)	5/135 (3)	6.5 (0.7, 12.2)	0.0278
		HBeAg seroconversion, n (%)	11/141 (8)	4/145 (3)	5.0 (–0.1, 10.2)	0.06
		Complete virological response: HBV DNA <0.7 MEq/mL by bDNA and loss of HBeAg, n (%)	13/141 (9)	1/145 (<1)	8.5 (3.6, 13.5)	0.0008
		Partial response: HBV DNA <0.7 MEq/mL, no HbeAg loss	80 (57)	7 (5)		
		Nonresponse: HBV DNA >0.7 MEq/mL	40 (28)	121 (83)		
		[redacted]				
		[redacted]	[redacted]	[redacted]		
		Year 2 Cohort, EOD, in partial virological responders: [redacted] [1]	n=77	n=3		
		HBV DNA <300 copies/mL by PCR at EOD (%)[1]	31 (40)	0 (0)		
		[redacted]	[redacted]	[redacted]		
		ALT ≤1.0×ULN (%)[1]	62 (81)	0 (0)		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]		
		Cumulative confirmed endpoints*, week 96 (all treated patients): [redacted] [1]				
		HBV DNA <300 copies/mL by PCR	42/141 (30) [1] [redacted]	[redacted]	[redacted]	[redacted]
		ALT ≤1.0×ULN (%)	120/141 (85) [1] [redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Cumulative proportion of treated patients who ever achieved a confirmed endpoint on-treatment; a confirmed endpoint is when 2 sequential measurements meet the success criteria (or last observation).
ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHB: chronic hepatitis B; CSR: clinical study report; EOD: end of dosing; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; qd: once daily; ULN: upper limit of normal.

014: A randomized, double-blind comparison of three doses of entecavir versus lamivudine in immunocompetent subjects with chronic hepatitis B infection with viremia on lamivudine therapy[64 65]

Results of the primary outcome and key secondary outcomes that relate to the measures specified in the decision problem are presented below. Detailed results are presented in Table 5.9.

Primary outcome

The primary efficacy endpoint was the proportion of patients with undetectable HBV DNA (<0.7 MEq/mL by bDNA) at week 24.

Primary outcome: Virological response at week 48: HBV DNA <0.7 MEq/mL by bDNA

Results: At week 24, 1.0 mg entecavir was superior to lamivudine with regard to viral load reduction in lamivudine-refractory patients[64]

	Entecavir 1.0 mg N=42	Lamivudine 100 mg N=45	p-value
n (%)	33/42 (79)	6/45 (13)	<0.0001

Key secondary outcomes

The secondary efficacy endpoints of the study at weeks 24 and 48 included: the reduction in HBV DNA level from baseline, the proportion of patients with undetectable HBV DNA (i.e. below LLOQ of 0.7 MEq/mL or 700,000 copies/mL or 2.5 pg/mL) by bDNA assay and by PCR assay (400 copies/mL); the decrease in the Ishak fibrosis score; HBeAg loss and seroconversion; normalisation of serum ALT; incidence of emerging genotypic changes in HBV isolates. Additional assessments included 24-week post-treatment responses.

Key secondary outcomes: At week 48: HBV DNA <400 copies/mL by PCR (virological response), ALT ≤1.0×ULN (biochemical response), HBeAg seroconversion.

Results: At week 48: 1.0 mg entecavir was superior to lamivudine in both virological and biochemical responses in lamivudine-refractory patients.

	Entecavir 0.5 mg	Lamivudine 100 mg	p-value
Virological response, n (%)[64]	11/42 (26)	2/45 (4)	<0.01
Biochemical response, n (%)[64]	19/28 (68)	2/33 (6)	<0.0001
HBeAg seroconversion, n (%)[64]	1/27 (4)	2/32 (6)	–

Table 5.9: Study 014 – Summary of results

Study design[64]	Population[64]	Endpoints	Results			
Dose-ranging, randomised, double-blind, active comparator Entecavir 0.1, 0.5 and 1.0 mg qd versus lamivudine 100 mg qd 52 weeks (with extended open-label entecavir 1.0 mg treatment for patients with a partial virological response at 48 weeks)	CHB patients with recurrent viremia on lamivudine		**Entecavir 1.0 mg**	**Lamivudine 100 mg**	**Difference (entecavir–lamivudine)**	**p-value**
		Week 24:[64]	N=141	N=145	(95% CI)	
		Primary endpoint: HBV DNA <0.7 MEq/mL by bDNA, n (%)	**33/42 (79)**	**6/45 (13)**		**<0.0001**
		Mean (SE) change HBV DNA by PCR (log_{10} copies/mL)	–4.21 (0.260)	–0.95 (0.25)		<0.0001
		ALT < 1.25×ULN (%)	11/28 (39)	7/33 (21)		–
		Complete virological response: HBV DNA <0.7 MEq/mL and loss of HBeAg and ALT <1.25×ULN (NC=F), n (%)	8/42 (19)	3/45 (7)	12.4 (–1.6, 26.4)	0.08
		Week 48:[64]	n=42	n=45		
		HBV DNA < 400 copies/mL by PCR	11(26)	2(4)		<0.01
		Mean (SE) change HBV DNA by PCR (log_{10} copies/mL)	–5.06 (0.25)	–1.37 (0.42)		<0.0001
		ALT <1.25×ULN (%)	19/28 (68)	2/33 (6)		<0.0001
		Loss of HBeAg, n (%)	3/27 (11)	3/32 (9)		–
		HbeAg seroconversion, n (%)	1/27 (4)	2/32 (6)		–
		Complete virological response: HBV DNA <0.7 Meq/mL and loss of HbeAg and ALT <1.25×ULN (NC=F), n (%)	12/42 (29)	2/45 (4)	24.1 (8.7, 39.6)	≤0.01 overall
		Complete response in patients who were HbeAg-positive at baseline	2/27 (7)	2/32 (6)		
		Complete response in patients who were HbeAg-negative at baseline	10/15 (67)	0/13 (0)		

ALT: alanine aminotransferase; bDNA: branched-chain DNA; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; qd: once daily; ULN: upper limit of normal.

5.5 Meta-analysis

A network meta-analysis (which included all relevant entecavir trials reported in Sections 5.3 and 5.4) was performed and is reported in Section 5.6.

5.6 Indirect/mixed treatment comparisons

The comparators specified in the decision problem of this analysis include lamivudine, pegIFNα-2a and telbivudine for the evaluation of entecavir in NA-naïve patients and ADV/LDV combination for patients who do not respond to lamivudine monotherapy. As there were no trials including all treatment options in any of the patient populations, a series of network meta-analysis were conducted.

5.6.1 Summary

The network meta-analyses were implemented as Bayesian hierachical models and assumed that treatment effects were exchangeable on the log-odds scale. The models used entecavir as the baseline treatment as it is common to all analyses. Estimates of both the log-odds ratio compared with entecavir and the absolute probabilities were obtained. The absolute probabilities were estimated using the average rate observed across the entecavir arms as a baseline. The models all assumed fixed treatment effects. This form of analysis is discussed in more detail by a number of authors.

5.6.2 Study selection

The studies identified during the systematic review of clinical effectiveness were interrogated to assess whether they contained information relevant to the network meta-analysis (see Appendix 8.4).

5.6.3 Analyses undertaken

Where possible, separate networks corresponding to different treatment periods were generated for the following endpoints:

- Proportion of patients with undetectable viral load below the LLOQ by PCR. Two limits were used in the network meta-analysis. [1]
- Proportion of patients achieving HBeAg seroconversion.
- Proportion of patients with histological improvement.
- Proportion of patients with ALT normalisation.

The 1-year analyses included data reported at either 48 or 52 weeks, while the 2-year analyses contained data reported at either 96 or 104 weeks. Inadequate data meant that analyses for any subsequent years were not possible. The source data used for the analyses are included in Appendix 8.4.

[1] 300 copies/mL and 400 copies/mL where data for the former was not available. The difference in the proportion of patients achieving undetectable viral load between the limits of 300 and 400 copies/mL appears negligible and allows for like-for-like indirect comparisons to be made.

5.6.4 Results

The results of the network meta-analysis for the different patient populations are shown in the tables below. The values represent the predicted probability of achieving the endpoint in question. The log-odds and odds ratios used to generate these probabilities are reported in Appendix 8.4. Year 2 predicted probabilities relate to cumulative rather than annual values, i.e. the proportion that have experienced the event at some point by the end of year 2 rather than the proportion who experienced the event during year 2. Entries in all tables marked "–" were not possible due to either a lack of data or an incomplete network.

HBeAg-positive, treatment-naïve patients

Tables 5.10 and 5.11 present the predicted probabilities and 95% CIs from the network meta-analysis. Not all individuals followed up during year 2 underwent a histological analysis, and therefore the patient counts for this endpoint are very small. Due to the extremely poor quality of the data, histological improvement was not analysed at year 2.

Table 5.10: Year 1 results from the network meta-analysis for HBeAg-positive, treatment-naïve patients (predicted probabilities, 95% CI)

Intervention	Undetectable viral load	HBeAg seroconversion	Histological improvement	ALT normalisation
Entecavir	68.8% (65.1, 72.4)	18.3% (15.4, 21.4)	71.9% (66.9, 76.8)	76.3% (72.9, 79.6)
Lamivudine	35.3% (28.8, 42.2)	18.3% (13.5, 24.0)	61.9% (51.9, 71.3)	66.4% (59.0, 73.4)
PegIFNα-2a	21.8% (14.5, 30.5)	24.5% (15.9, 35.3)	–	43.9% (32.6, 55.7)
Telbivudine	55.7% (46.1, 65.0)	19.7% (13.1, 27.7)	71.8% (60.8, 81.1)	68.8% (59.3, 77.3)

ALT: alanine aminotransferase; CI: confidence interval; HBeAg: hepatitis B e antigen; PegIFN: pegylated interferon

Table 5.11: Year 2 results from the network meta-analysis for HBeAg-positive, treatment-naïve patients (predicted probabilities, 95% CI)

Intervention	Undetectable viral load	HBeAg seroconversion	ALT normalisation
Entecavir	78.8% (75.3, 82.0)	26.8% (23.2, 30.5)	90.2% (87.6, 92.4)
Lamivudine	39.2% (31.7, 47.3)	24.2% (18.6, 30.5)	83.6% (76.8, 89.1)
PegIFNα-2a	–	–	–
Telbivudine	56.2% (45.8, 66.2)	29.1% (20.8, 38.5)	87.8% (81.4, 92.6)

ALT: alanine aminotransferase; CI: confidence interval; HBeAg: hepatitis B e antigen; PegIFN: pegylated interferon

In HBeAg-positive patients, entecavir was significantly better than lamivudine, pegIFN and telbivudine in achieving undetectable HBV DNA levels in years 1 and 2. Entecavir was equivalent to lamivudine, pegIFN and telbivudine on HBeAg seroconversion

endpoint. On ALT normalisation, entecavir performed significantly better than lamivudine and pegIFN in years 1 and 2 and was equivalent to telbivudine. In terms of histological improvement, entecavir was significantly better than lamivudine and was equivalent to telbivudine

HBeAg-negative, treatment-naïve patients

Tables 5.12 and 5.13 present the predicted probabilities and 95% CIs from the network meta-analysis. Again, histological improvement was not analysed at year 2.

Table 5.12: Year 1 results from the network meta-analysis for HBeAg-negative, treatment-naïve patients (predicted probabilities, 95% CI)

Intervention	Undetectable viral load	Histological improvement	ALT normalisation
Entecavir	90.5% (87.3, 93.3)	70.3% (65.0, 75.3)	79.3% (75.0, 83.4)
Lamivudine	71.5% (59.6, 81.5)	60.6% (50.3, 70.1)	71.2% (62.0,79.3)
PegIFNα-2a	61.0% (43.8, 76.2)	–	36.2% (23.0, 51.0)
Telbivudine	87.9% (78.4, 94.1)	61.4% (47.0, 74.6)	64.8% (50.0,77.4)

ALT: alanine aminotransferase; CI: confidence interval; HBeAg: hepatitis B e antigen; PegIFN: pegylated interferon

Table 5.13: Year 2 results from the network meta-analysis for HBeAg-negative, treatment-naïve patients (predicted probabilities, 95% CI)

Intervention	Undetectable viral load	HBeAg seroconversion	ALT normalisation
Entecavir	93.9% (91.2, 96.1)	–	90.0% (86.6,92.9)
Lamivudine	77.1% (64.2, 87.1)	–	84.4% (75.8, 90.8)
PegIFNα-2a	–	–	–
Telbivudine	91.8% (84.3, 96.4)	–	88.9% (80.6, 94.5)

ALT: alanine aminotransferase; CI: confidence interval; HBeAg: hepatitis B e antigen; PegIFN: pegylated interferon

In HBeAg-negative patients, entecavir was significantly better than lamivudine and pegIFN in achieving undetectable HBV DNA levels in years 1 and 2 and was equivalent to telbivudine. On ALT normalisation, entecavir was significantly better than lamivudine, pegIFN and telbivudine in year 1. In terms of histological improvement, entecavir was significantly better than lamivudine and equivalent to telbivudine.

HBeAg-positive, lamivudine-resistant patients

Information on this patient group is in general not as prevalent as for individuals who are treatment-naïve. The trials that have been carried out also tend to be a lot smaller than

the trials undertaken in naïve individuals and so the likelihood of an event not occurring in one of the arms is a lot higher. For these reasons, it was felt that while there were some possible networks, these would be unstable and consequently the results not clinically meaningful. Therefore, a network analysis was not performed in this patient group.

As such a simple comparison was conducted using lamivudine 100mg as the common reference. This is presented in section 5.6.5.

5.6.5 An indirect comparison of the efficacy entecavir versus adefovir/lamivudine in HBeAg positive lamivudine refractory CHB Patients

Table 5.14: An indirect comparison of the efficacy entacavir with adefovir/ lamivudine in HBeAg lamivudine refractory CHB Patients

Studies	AI-463-026[62]			Perrillo et al [69]			Peters et al 2004[70]		
Efficacy Endpoint	ETV (1.0mg) N=141	LMV (100mg) N=145	p-value	ADV(10mg) /LMV (100mg)	LMV (100mg)	p-value	ADV(10mg) /LMV (100mg) N=19	LMV (100mg) N=19	p-value
Undetectable HBV DNA (<300 copies/ml) (%)	19	1	< 0.0001	20	0	< 0.01	NA[1]	NA[1]	<0.001
HBeAg seroconversion (%)	8	3	0.06	8	2	Not signicant	6	0	0.152
ALT normalisation (%)	75	23	< 0.0001	30	6	0.002	47	5	0.004

[1] Peters et al reported HBV DNA < 1000 copies/ml (35% for ADV/LMV combination vs. 0% for LMV only)

Table 5.1.4 presents evidence from 3 main studies, AI463026, Peters et al. and Perrillo et al. Efficacy endpoints common to the 3 studies were percentage of patients with undetectable HBV DNA level, percentage of patients with HBeAg seroconversion and percentage of patients with ALT normalisation,

Although appropriate for comparison, studies AI463-026 and Peters et al. differ markedly in the number of participants: 286 treated in the ETV study versus 59 and 95 treated in the Peters and Perrillo studies respectively. The ETV study includes histological improvement as a co-primary endpoint; liver biopsy was not performed in the Peters and Perrillo studies.

In study AI463-026, ETV was superior to LMV 100mg for the endpoints of cases of undetectable HBV DNA, cases with ALT normalisation, and HBeAg seroconversion clearly demonstrating the effectiveness of ETV 1.0mg in LMV-refractory patients.

In the study by Peters and Perrillo studies, ADV10mg/LMV100mg was superior to LMV 100mg for the common endpoints of cases of undetectable HBV DNA, cases with ALT normalisation – also demonstrating the efficacy of ADV/LMV in LMV refractory patients.

5.6.6 A descriptive analysis of the rates of genotypic resistance across antiviral therapies

Resistance rates are routinely evaluated in long-term open-label extensions of RCTs and reported as cumulative rates of resistance. Head-to-head studies evaluating the relative rates of genotypic resistance are not available. Similarly a formal network meta-analysis of resistance rates was not possible because the data come from non-RCT and the patient populations were too heterogeneous. However, a descriptive analysis of the rates of genotypic resistance across available NAs taken from the available literature is presented below.

Table 5.15: An indirect comparison of the cumulative rates of genotypic resistance to the available NAs

	Cumulative rates of genotypic resistance (%) in NA-naïve patients [a]				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Entecavir [68,67] HBeAg-positive/-negative	0.2	0.5	1.2	1.2	–
Lamivudine [71 23] HBeAg-positive SmPC	 23 24	 46 –	 55 –	 71 67	 65 [b] –
Adefovir[24] HBeAg-negative	0	3	11	18	29
Telbivudine[5 72 73]**,** HbeAg-positive HbeAg-negative	 3-4 2-3	 22 9	 – –	 – –	 – –

[a] Note that there are differences in populations and methodologies.
[b] Annual prevalence.
HBeAg: hepatitis B e antigen; NA: nucleo(s/t)ide analogue.

Lamivudine and telbivudine show high rates of genotypic resistance. Adefovir rates of resistance are 0% at year 1 but increase to 29% by year 5. Entecavir shows two resistance patterns: low rates of resistance in lamivudine-naïve patients out to year 4 (cumulative rate of 1.2%), but increasing rates in a lamivudine-refractory population.

Current AASLD guidelines state that, among the approved NA therapies for CHB, lamivudine is associated with the highest and entecavir with the lowest rate of drug resistance in NA-naïve patients[5]; this is reflected in the descriptive analysis above.

5.7 Safety

Safety evidence in this section is presented from;

1. Relevant RCTs cited to demonstrate efficacy (022, 027, 023, 026, 014)
2. The summary of safety information presented within the SmPC[1]

5.7.1 Safety evidence from individual RCTs

In Tables 5.16–5.20 the outcomes related to safety and tolerability during treatment with entecavir versus lamivudine in the relevant RCTs are summarised. The frequencies of adverse events and serious adverse events were similar in the entecavir and lamivudine treatment groups.

Table 5.16: Study 022 – summary of safety[56]

Timing and event	Entecavir 0.5 mg (N=354)	Lamivudine 100 mg (N=355)	p-value
During 48-week treatment			
Any adverse event, n (%)	306 (86)	297 (84)	0.34
Serious adverse event, n (%)	27 (8)	30 (8)	0.78
Discontinuation due to adverse event, n (%)	1 (<1)	9 (3)	0.02
ALT >2×baseline and >10×ULN, n (%) [a]	12 (3)	23 (6)	0.08
ALT >2×baseline and >5×ULN, n (%) [b]	37 (10)	59 (17)	0.02
Death, n (%)	0 (0)	2 (<1)	0.50
Post-treatment follow-up [c]			
ALT >2×reference value and >10×ULN [d]	2 (1)	9 (7)	0.03
ALT >2×reference value and >5×ULN [b]	3 (2)	16 (12)	0.002

[a] According to the protocol, these findings constituted the definition of an ALT flare during treatment.
[b] The analysis was conducted post hoc.
[c] 134 patients in the entecavir group and 129 in the lamivudine group had entered post-treatment follow-up at the time of database lock.
[d] According to the protocol, these findings constituted the definition of a post-treatment ALT flare. The reference level was the lesser of the baseline and end-of-treatment ALT values.
ALT: alanine aminotransferase; ULN: upper limit of normal.

Table 5.17: Study 027 – summary of safety[58]

Timing and event	Entecavir 0.5 mg (N=325)	Lamivudine 100 mg (N=313)	p-value
During 48-week treatment			
Any adverse event, n (%)	246 (76)	248 (79)	0.30
Serious adverse event, n (%)	21 (6)	24 (8)	0.64
Discontinuation due to adverse event, n (%)	6 (2)	9 (3)	0.44
ALT >2×baseline and >10×ULN, n (%) [a]	3 (<1)	5 (2)	0.50
ALT >2×baseline and >5×ULN, n (%) [b]	6 (2)	10 (3)	0.32
Death, n (%)	2 (<1)	0 (0)	0.50
Post-treatment follow-up [c]			
ALT >2× reference value and >10× ULN [d]	23 (8)	29 (11)	0.19
ALT > 2× reference value and >5× ULN [b]	36 (12)	77 (29)	<0.001

[a] According to the protocol, these findings constituted the definition of an ALT flare during treatment.
[b] The analysis was conducted post hoc.
[c] 297 patients in the entecavir group and 263 in the lamivudine group had entered post-treatment follow-up at the time of database lock.
[d] According to the protocol, these findings constituted the definition of a post-treatment ALT flare. The reference level was the lesser of the baseline and end-of-treatment ALT values.
ALT: alanine aminotransferase; ULN: upper limit of normal.

Table 5.18: Study 023 – summary of safety[60]

Timing and event	Entecavir 0.5 mg (N=258)	Lamivudine 100 mg (N=261)
During 48-week treatment		
Any adverse event, n (%)	154 (60)	145 (56)
Serious adverse event, n (%)	9 (3)	12 (5)
Discontinuation due to adverse event, n (%)	1 (<1)	3 (1)
ALT >2×baseline and >10×ULN, n (%)	11 (4)	15 (6)
Death, n (%)	0 (0)	0 (0)

ALT: alanine aminotransferase; ULN: upper limit of normal.

Table 5.19: Study 026 – summary of safety[62]

Timing and event	Entecavir 1 mg (N=141)	Lamivudine 100 mg (N=145)
During 48-week treatment		
Any adverse event, n (%)	120 (85)	117 (81)
Serious adverse event, n (%)	14 (10)	11 (8)
Discontinuation due to adverse event, n (%)	2 (1)	10 (7)
ALT >2×baseline and >10×ULN, n (%)	1 (<1)	16 (11)
Death, n (%)	1 (<1)	2 (1)

ALT: alanine aminotransferase; ULN: upper limit of normal.

Table 5.20: Study 014 – summary of safety[64]

Timing and event	Entecavir 1 mg (N=42)	Lamivudine 100 mg (N=45)
During 48-week treatment		
Any adverse event, n (%) [a]	36 (86)	38 (84)
Serious adverse event, n (%)	5 (12)	3 (7)
Discontinuation due to adverse event, n (%)	3 (7)	4 (9)
ALT >2×baseline, n (%)	7 (17)	15 (33)
Death, n (%)	0 (0)	0 (0)
Post-treatment follow-up		
ALT >2×reference value, n	7/18	3/12
Death, n (%)	0 (0)	0 (0)

[a] Including laboratory abnormalities reported by the investigator as an adverse event.
ALT: alanine aminotransferase.

5.7.2 Safety summary presented in the SmPC[1]

The summary of safety information presented within the SmPC is reproduced here.

Assessment of adverse reactions is based on four clinical studies in which 1,720 patients with CHB infection received double-blind treatment with entecavir 0.5 mg/day (n=679), entecavir 1 mg/day (n=183) or lamivudine (n=858) for up to 107 weeks. The safety profiles of entecavir and lamivudine, including laboratory test abnormalities, were comparable in these studies.

The most common adverse reactions of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%).

Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class. Frequency is defined as “very common” (≥1/10) or “common” (≥1/100, <1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Experience in NA-naïve patients (HBeAg-positive and -negative)
The safety profile is based on treatment exposure to entecavir 0.5 mg once daily for a median of 53 weeks.

Psychiatric disorders:	(common) insomnia
Nervous system disorders:	(common) headache, dizziness, somnolence
Gastrointestinal disorders:	(common) vomiting, diarrhoea, nausea, dyspepsia
General disorders and administration site conditions:	(common) fatigue

Laboratory test abnormalities: 2% of patients had ALT elevations both >10×ULN and >2×baseline, 5% had ALT elevations >3×baseline and <1% had ALT elevations >2×baseline together with total bilirubin >2×ULN and >2×baseline. Albumin levels <2.5 g/dL occurred in <1% of patients, amylase levels >3×baseline in 2%, lipase levels >3×baseline in 11% and platelets <50,000/mm^3 in <1%.

Treatment beyond 48 weeks: continued treatment with entecavir for a median duration of 96 weeks did not reveal any new safety signals.

Experience in lamivudine-refractory patients

The safety profile is based on treatment exposure to entecavir 1 mg once daily for a median of 69 weeks.

Psychiatric disorders:	(common) insomnia
Nervous system disorders:	(very common) headache (common) dizziness, somnolence
Gastrointestinal disorders:	(common) vomiting, diarrhoea, nausea, dyspepsia
General disorders and administration site conditions:	(common) fatigue

Laboratory test abnormalities: 2% of patients had ALT elevations both >10×ULN and >2×baseline, 4% had ALT elevations >3×baseline and <1% had ALT elevations >2×baseline together with total bilirubin >2×ULN and >2×baseline. Amylase levels >3×baseline occurred in 2%, lipase levels >3×baseline in 18% and platelets <50,000/mm^3 in <1%.

Treatment beyond 48 weeks: continued treatment with entecavir for a median duration of 96 weeks did not reveal any new safety signals.

Exacerbations during treatment

In studies with NA-naïve patients, on-treatment ALT elevations >10×ULN and >2×baseline occurred in 2% of entecavir-treated patients versus 4% of lamivudine-treated patients. In studies with lamivudine-refractory patients, on-treatment ALT elevations >10×ULN and >2×baseline occurred in 2% of entecavir-treated patients versus 11% of lamivudine-treated patients. Among entecavir-treated patients, on-treatment ALT elevations had a median time to onset of 4–5 weeks, generally resolved with continued treatment, and, in the majority of cases, were associated with a ≥2 $\log_{10}$/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations after discontinuation of treatment

Acute exacerbations of hepatitis have been reported in patients who have discontinued anti-HBV therapy, including therapy with entecavir. In studies in NA-naïve patients, 6% of entecavir-treated patients and 10% of lamivudine-treated patients experienced ALT

elevations (>10×ULN and >2×reference [minimum of baseline or last EOD measurement]) during post-treatment follow-up. Among entecavir-treated NA-naïve patients, ALT elevations had a median time to onset of 23–24 weeks, and 86% (24/28) of ALT elevations occurred in HBeAg-negative patients. In studies in lamivudine-refractory patients, with only limited numbers of patients being followed up, 11% of entecavir-treated patients and no lamivudine-treated patients developed ALT elevations during post-treatment follow-up.

In the clinical trials entecavir treatment was discontinued if patients achieved a prespecified response. If treatment is discontinued without regard to treatment response, the rate of post-treatment ALT flares could be higher.

Experience in patients co-infected with HIV
The safety profile of entecavir in a limited number of HIV/HBV co-infected patients on lamivudine-containing highly-active antiretroviral therapy (HAART) regimens was similar to the safety profile in mono-infected HBV patients.

Gender/age
There was no apparent difference in the safety profile of entecavir with respect to gender (approx. 25% women in the clinical trials) or age (approx. 5% of patients >65 years of age).

Decompensated cirrhosis
A higher rate of serious hepatic adverse events has been observed in patients with decompensated cirrhosis compared with rates in patients with compensated liver function. This observation is based on limited experience in 45 patients with Child–Pugh score ≥7 at the start of entecavir treatment.

5.8 Non-RCT evidence

Summary information on the methodology and results of the relevant non-RCT evidence relevant to the decision problem is presented below. In addition, details of methods, critical appraisal and results are presented in tabular form in Sections 5.8.3, 5.8.4, and 5.8.5.

5.8.1 Study 901 – 4-year treatment cohort[66]

An open-label extension of study 022 to evaluate long-term efficacy/safety of entecavir through 4 years in NA-naïve, HBeAg-positive CHB patients is presented.

Patients

The NA-naïve, HBeAg-positive entecavir 4-year treatment cohort consisted of 183 entecavir-treated patients from study 022 who were enrolled in study 901 with a ≤35 day gap in treatment between the two studies to ensure continuous exposure to drug.

This analysis cohort was defined without regard to either treatment response at EOD in study 022 or HBV DNA, ALT measurements or HBV serology at the start of dosing in study 901. Initially, due to ongoing blinding of studies 022 and 027, patients enrolling in study 901 received a combination of entecavir 1 mg and lamivudine 100 mg daily. The protocol was subsequently amended for patients to receive monotherapy with entecavir 1 mg daily.

Results

Results from the NA-naïve, HBeAg-positive entecavir 4-year treatment cohort demonstrate that patients continue to derive benefit from extended entecavir therapy, with 91% of patients maintaining undetectable HBV DNA through 4 years of treatment[66].

5.8.2 Entecavir resistance monitoring programme[67 68]

The results of the entecavir-resistance monitoring program are presented to week 192 (Year 4) for entecavir-treated patients in six entecavir clinical studies. Studies 022 and 027 were conducted in NA-naïve patients, while studies 026 and 014 (1.0 mg once daily entecavir) and 015 (in orthotopic liver transplant recipients) were conducted in lamivudine-refractory patients. Treatment in all these studies was often continued in study 901. Results are reported by patient type: NA-naïve or lamivudine-refractory as this is clinically relevant.

Patient selection

Patients monitored for resistance included all those initially randomised into a 0.5 mg entecavir treatment arm for NA-naïve patients and a 1.0 mg entecavir treatment arm for lamivudine-refractory patients. At the end of dosing in the Phase 2 and 3 studies, some patients received therapy in rollover study 901. Risk for resistance assumes continuous drug pressure on viral replication. Thus the resistance cohort only included patient data and samples in study 901 from those considered as receiving “continuous treatment”. That is, visits and samples from 901 were included in the resistance analysis only if the treatment interruption between the end of dosing (EOD) in the original study and the start of dosing in 901 was ≤5 weeks (35 days). When treatment gaps exceeded 35 days, EOD was considered the last treatment date prior to the gap.

Inclusion of data from the rollover study 901 for continuously treated patients resulted in a subset of patients who received an entecavir dose regimen that differed from their original study. Since treatment arms were blinded at the time of rollover for most patients, study 901 included a combination of 0.5 mg entecavir and 100 mg lamivudine. Amendments to the 901 protocol resulted in changing the therapy to 1.0 mg entecavir with 100 mg lamivudine and then 1.0 mg entecavir monotherapy. To ensure the effect of drug pressure was observed, only patients with an HBV DNA assessment by PCR at baseline and at or beyond the windowed week 24 timepoint were included.

Resistance monitoring

The primary strategy employed for entecavir resistance surveillance involved monitoring of HBV DNA by PCR to identify patients who had detectable HBV DNA despite at least 24 weeks of therapy, and those experiencing virological breakthrough. In addition, paired baseline and on-treatment samples from all patients with PCR detectable HBV DNA at weeks 48, 96, 144, 192 or at EOD within years 1, 2, 3 or 4 were isolated and subjected to genotyping in the form of nucleotide sequencing. Thus, all entecavir-treated patients with HBV DNA levels >300 copies/mL at weeks 48, 96, 144 or EOD had paired samples genotyped. Phenotype was determined for all emerging substitutions. All patients experiencing a virological rebound (≥1 $\log_{10}$ increase from nadir), including those with no observed genotypic changes, were phenotyped

Results[67 68]

In these studies a total of 871 patients were included in the ITT populations. Of these 850 patients (663 NA-naïve, 187 lamivudine-refractory) were treated for 48 weeks and monitored for resistance. For 749 patients genotypic analysis was performed on baseline samples and on all evaluable samples (HBV DNA levels >300 copies/mL) at weeks 48, 96, 144, 192 or EOD.

Resistance rates in NA-naïve patients

The cumulative probability of genotypic resistance is 1.18% after 4 years of treatment. The cumulative probability of virological rebound due to entecavir resistance through 4 years of therapy is 0.82%. Entecavir resistance is rare in NA-naïve patients due to rapid and sustained DNA suppression of serum HBV DNA and a high genetic barrier to resistance requiring three or more subtitutions in the polymerase genome. [67]

Resistance rates in lamivudine-refractory patients

Lamivudine-refractory patients demonstrate increased rates of resistance when compared with NA-naïve patients due to a decrease in the genetic barrier to resistance. The cumulative probability of genotypic resistance is 46% through 4 years of treatment, and the cumulative probability of virological rebound due to entecavir resistance through 4 years of therapy is 41%.[67]

5.8.3 Summary of methodology of relevant non-RCT evidence

Trial no.; reference	Intervention	Comparator	Participants	Duration	Study type	Outcome measures
901[66]; Preliminary assessment of safety and antiviral activity of open-label entecavir in subjects with chronic hepatitis B following monotherapy in 022	In 022 ; Entecavir 0.5mg In 901; Entecavir 1 mg (Entevavir 1mg plus lamivudine 100mg)	Nil all patients received entecavir	This 4-year continuous treatment descriptive cohort is an extension of the double-blind phase of the 022 study. Patients included in the analysis: • continued on-treatment in study 022 through year 2 • had HBV DNA <0.7 MEq/mL by bDNA • were HBeAg-positive at week 96 (end of study 022) • were enrolled in study 901 with a ≤35 day gap in treatment following EOD in study 022 • had HBV DNA measurements by PCR at week 144.	A 4-year extension to study 022 is presented.	Open-label	Safety DNA suppression ALT normalisation HBeAg loss HBeAg seroconversion
Entecavir-resistance 4-year monitoring programme[67 68]	In RCTs; NA-naïve patients treated with 0.5 mg entecavir; lamivudine-refractory patients treated with 1.0 mg In study 901; 0.5 or 1.0 mg entecavir + 100 mg lamivudine, or 1.0 mg entecavir only	Nil all patients received entecavir	NA-naïve and LVD-refractory CHB patients treatedvwith entecavir in 022, 027, 014, 015 and 901 with treatment gap of ≤35 days	Results from a 4 year monitoring programme are presented	Open-label	Subjects at risk of ETVr; subjects with detected ETVr; subjects at risk of ETVr and virological breakthrough; subjects with detected ETVr and breakthrough; cumulative probability of emerging genotypic ETVr; cumulative probability of ETVr and breakthrough

5.8.4 Critical appraisal of relevant non-RCTs

Study	Design constraints
901[68]	• Open-label, uncontrolled, nonrandomised, descriptive. • Patients enrolled from 022 into 901 - initially received combination of entecavir 1 mg and lamivudine 100 mg, then amended to entecavir 1mg monotherapy
Entecavir-resistance 4-year monitoring programme[67 68]	• Open-label, uncontrolled, non-randomised, descriptive. • Patients enrolled from RCTs into 901- initially received combination of entecavir 0.5mg and lamivudine 100mg, then amended to receive combination of entecavir 1 mg and lamivudine 100 then amended to receive entecavir 1mg monotherapy, with treatment gap of <35 days

5.8.5 Summary of results of relevant non-RCT evidence

Trial no.; reference	Drug dosages	Patient numbers	Outcome measures	Clinical results for the 4-year cohort				
901[66] - 4 year treatment cohort (022 extension)	In 022; 0.5 mg entecavir In study 901: Entecavir 1 mg (Entevavir plus lamivudine 100mg)	183	• DNA<300 copies/mL • ALT ≤1.0xULN • HBeAg loss • HBeAg seroconversion	**Measure**	**Year 1**	**Year 2**	**Year 3**	**Year 4**
				DNA <300 copies/mL	80/146 (55)	116/140 (83)	116/131 (89)	98/108 (91)
				ALT ≤1.0xULN	95/146 (65)	109/140 (78)	103/134 (77)	96/112 (86)
				HBeAg loss	0%	0%	39/96 (41)	
				HBeAg seroconversion	0%	0%	15/96 (16)	
Entecavir-resistance 4-year monitoring program[67] [68]	In RCTs; 0.5 mg entecavir or 1.0 mg In study 901: -0.5mg entecavir + 100 mg lamivudine, -1mg entecavir + 100 mg lamivudine, -1.0 mg entecavir only	749	• Cumulative probability of emerging genotypic ETVr • Cumulative probability of ETVr [c] and virological breakthrough	**NA-naïve studies**[67]	**Year 1 N =663**	**Year 2 N=278**	**Year 3 [a1] N=149**	**Year 4 N=120**
				Patients treated and monitored for resistance [b]	663	278	149	120
				Cumulative probability of emerging genotypic ETVr [c]	0.15%	0.51%	1.18%	1.18%
				Cumulative probability of ETVr [c] and virological breakthrough[d]	0.15%	0.15%	0.82%	0.82%
				Lamivudine-refractory studies[67]	**Year 1 N=187**	**Year 2 N=146**	**Year 3 [a2] N=80**	**Year 4 N=53**
				Patients treated and monitored for resistance [b]	187	146	80	53
				Cumulative probability of emerging genotypic ETVr [c]	6.21%	15.01%	36.26%	46.32%
				Cumulative probability of ETVr [c] and virological breakthrough [d]	1.07%	10.69%	27.04%	41.01%

[a1] Results in Year 3/4 reflect use of a 1-mg dose of entecavir for 147/149 patients and of combination entecavir-lamivudine therapy for a medianof 20 weeks (followed by long-term entecavir therapy) for 130/149 patients in a rollover study.

[a2] Results in Year 3/4 reflect use of combination entecavir-lamivudine therapy for a median of 13 weeks (followed by long-term entecavir therapy) for 48/80 patients 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), or after week 102 through week 156 (Year 3).

[c] Patients also have LVDr substitutions.

ALT: alanine aminotransferase; ETVr: entecavir-resistant mutations; HBV: hepatitis B virus; LVDr: lamivudine-resistant mutations; PCR: polymerase chain reaction; ULN: upper limit of normal.

5.9 Interpretation of clinical evidence

5.9.1 Relevance of the evidence base to the decision problem

Comparison with lamivudine in NA-naïve CHB patients

Lamivudine, the first NA to have an indication for CHB, is currently the most widely used first-line therapy in treatment-naïve patients in the UK. Clinical evidence from three head-to-head RCTs in NA-naïve patients (022, 023, 027) shows the superior efficacy of entecavir compared with lamivudine, with comparable safety.

The 022 study, where patients were HBeAg-positive and NA-naïve, showed that entecavir had statistically significant superior histological improvement (primary endpoint), HBV DNA reduction and ALT normalisation compared with lamivudine. There was no significant difference in HBeAg seroconversion rates. Of entecavir patients who were virological-only responders and continued therapy with entecavir through 2 years, 81% achieved DNA <300 copies/mL, 79% achieved normalised ALT, and HBeAg loss was seen in 15%. Rates of adverse events, serious adverse events and discontinuations due to adverse events were similar between entecavir and lamivudine.

In the 027 study, where patients were HBeAg-negative and NA-naïve, entecavir showed superior histological improvement (primary endpoint) and a higher proportion of patients achieving undetectable HBV DNA compared with lamivudine. Rates of adverse events, serious adverse events and discontinuations due to adverse events were similar between the products. Continued benefit was seen in patients who continued entecavir treatment through to 2 years for HBV DNA suppression and ALT normalisation.

The 023 study, conducted in China, which included both HBeAg positive and HBeAg negative patients, also demonstrated superior efficacy for entecavir versus lamivudine.

Entecavir shows very low rates of resistance in NA-naïve patients due to a high genetic barrier and its rapid viral suppression. Cumulative rates of genotypic resistance at years 1, 2, 3 and 4 for entecavir are <1%, <1%, 1.2% and 1.2%, respectively. The cumulative rate of viral rebound due to resistance for entecavir remains <1% after 4 years. Resistance rates for lamivudine are considerably higher, with reported rates of 23-24% after 1 year and 65% after 5 years of therapy. Antiviral resistance carries the risk of restricting future treatment options and can lead to acute hepatic flares and disease progression with potential for increased healthcare utilisation.

The validity of the evidence base to the decision problem is endorsed by inclusion of the above study results into recently published external authoritative international guidelines. The updated AASLD guidelines include these results and indicate that preference should be given to agents that are highly potent and have a high barrier to resistance, namely entecavir and adefovir; these guidelines caution against the use of lamivudine and telbivudine in NA-naïve patients.

Clinical data from RCTs shows that entecavir is a clinically effective therapy in NA-naïve patients with very low rates of resistance and an acceptable safety profile when compared with lamivudine.

Comparison with telbivudine in NA-naïve CHB patients

Telbivudine is not widely used within the UK; however, it has been defined by NICE as a comparator in this submission. No direct RCT comparator data are available to entecavir; however, a network meta-analysis of data was performed.

Comparing entecavir and telbivudine in HBeAg positive patients after 1 year of treatment, the network meta-analysis shows entecavir to be superior in the probability of achieving undectable viral load. A comparison of cumulative genotypic resistance rates shows that entecavir is associated with lower genotypic resistance rates compared with telbivudine (0.5% vs. 22% at year 2 in HBeAg-positive patients; 0.5% vs. 9% at year 2 in HbeAg negative).

These high rates of resistance to telbivudine are recognised by the AASLD guidelines, which state that telbivudine is not a preferred antiviral agent for NA-naïve patients as compared with entecavir and adefovir due to its lower genetic barrier and lower potency.

Therefore, the network meta-analysis shows that entecavir has greater patient benefit than telbivudine for both HBeAg-positive and -negative NA-naïve patients in long-term use because of its superior resistance profile.

Comparison with pegIFNα-2a in treatment-naïve CHB patients

No direct RCT data are available for this comparison; therefore, a network meta-analysis was conducted for HBeAg-positive and HBeAg-negative treatment-naïve CHB patients. In HBeAg-positive patients, entecavir results in a significantly higher average predicted probability of viral suppression compared with pegIFN (Year 1: 68.8% [65.1–72.4] vs. 21.8% [14.5-30.5]). Entecavir was also superior to pegIFN in ALT normalisation (average predicted probabilities at year 1: 76.3% [72.9–79.6] vs. 43.9% [32.6–55.7]). HBeAg seroconversion rates were comparable, the mean predicted probabilities being 18.3% (15.4–21.4) vs. 24.5% (15.9–35.3) at year 1.

In HBeAg-negative patients, entecavir was superior to pegIFN in viral suppression (mean predicted probabilities: 90.5% [87.3–93.3] vs. 61% [43.8–76.2] at year 1), and ALT normalisation (79.3% [75.0–83.4] vs. 36.2% [23.0–51.0] at year 1). The role of pegIFN in the treatment of HBeAg-negative patients is questionable, given that only 19% of patients have a sustained response of DNA <400 copies/mL after 48 weeks of therapy and 24 weeks of follow-up.

PegIFN is well recognised to have significant tolerability issues. Adverse events were experienced by 88% of pegIFN-treated patients, compared with 53% of patients in a lamivudine comparator group from a well-controlled RCT. Furthermore, 6% of the pegIFN-treated patients and 4% of the lamivudine-treated patients experienced serious adverse events during the studies. Adverse events or laboratory abnormalities led to 5% of patients withdrawing from pegIFN treatment, while <1% of patients withdrew from lamivudine treatment for these reasons. Entecavir showed a similar safety profile to lamivudine in the 022 and 027 studies.

In summary, in both HBeAg-positive and HBeAg-negative patients entecavir is superior to pegIFN in viral suppression and ALT normalisation. In HBeAg-positive patients, entecavir is equivalent to pegIFN in rates of seroconversion. Entecavir and pegIFN are both possible treatment options for treatment-naïve HBeAg-positive patients. Given the relatively reduced efficacy in HBeAg-negative patients to pegIFN, entecavir should be preferred in these patients.

Comparison with lamivudine in lamivudine-refractory patients

A major limitation of lamivudine is the emergence of drug-resistant HBV. Clinical evidence from the largest RCT in this population shows superior efficacy of entecavir to continued lamivudine treatment in patients that are refractory to lamivudine.

The 026 study enrolled a particularly difficult population to treat: all patients were refractory to lamivudine treatment, had high levels of DNA (≥3 MEq/mL), with 85% having lamivudine resistance substitutions. All patients had persistence of HBeAg at baseline, even though they had all received lamivudine and 54% had failed prior IFN therapy. Entecavir demonstrated superior responses compared with lamivudine across histological, virological, serological (HBeAg loss) and biochemical endpoints to continued lamivudine at 48 weeks. In all, 40% of entecavir-treated, lamivudine-refractory, HBeAg-positive CHB patients who continued treatment into the second year of treatment achieved undetectable HBV DNA levels (<300 copies/mL)

Entecavir shows increasing rates of resistance in lamivudine-refractory patients when compared with NA-naïve patients. This is due to a decrease in the genetic barrier to resistance caused by the YMDD mutation. Cumulative rates of viral rebound with genotypic resistance in this population increase from 1% after 1 year to 41% through 4 years of treatment.

The validity of these results to the decision problem is reflected in the recently updated and published AASLD guidelines which suggest stopping lamivudine and starting entecavir in a lamivudine-resistant population as a clinical option. Thus the clinical data, suggests entecavir is a clinically effective therapy compared with continued lamivudine in the described population.

Comparison with adefovir dipivoxil/lamivudine in lamivudine-refractory CHB patients

No direct RCT comparator is available comparing entecavir to adefovir/lamivudine in a lamivudine-refractory CHB population. The provision of an indirect comparison is also difficult due to paucity of well controlled trials and different baseline population groups studied

The most widely used treatment stategy for lamivudine-refractory CHB patients in the UK is the early add-on strategy of adefovir to continued lamivudine therapy versus a switch to adefovir. The evidence base for this consists of a small RCT in HBeAg-negative patients, as well as uncontrolled observational data. The evidence suggests that adding on adefovir results in similar DNA suppression to adefovir monotherapy, but less resistance is reported in the add-on strategy. There is a lack of data for entecavir in the HBeAg-negative, lamivudine-refractory population

Limited data exists on HBeAg-positive, lamivudine-refractory CHB patients for adefovir. This is a more difficult population to treat than the HBeAg negative population as described in the paragraph above due to higher baseline DNA levels and persistence of HBeAg. Evidence from large trials is not available for the use of adefovir/lamivudine in this population. It is therefore difficult to address the decision problem based on available evidence and the mismatch in studied populations.

5.9.2 Applicability of study results to patients in routine clinical practice

The ultimate goal of HBV treatment is to induce remission of liver disease and prevent progression to cirrhosis and HCC. These long-term measures are not practical in a clinical trial setting and alternative biomarkers (e.g. histological, virological and biochemical endpoints) are required.

The EMEA CHMP document CPMP/EWP/6172/03 states that the assessment of histological response is considered an objective efficacy variable as it corresponds to the ultimate goal of therapy, i.e. to induce remission of liver disease[14]. Histological improvement was the primary measure for the entecavir Phase 3 programme.

AASLD guidelines state that quantification of serum HBV DNA is a crucial component in the evaluation of patients with CHB infection and in the assessment of the efficacy of antiviral treatment.[5] Large cohort studies have established the relationship between higher baseline HBV DNA and risk of disease progression. An RCT by Liaw et al. in lamivudine-treated patients established that those who maintained suppression to DNA had slower disease progression compared with those on placebo and patients who developed lamivudine resistance and subsequent virological breakthrough[46]. AASLD guidelines state that quantification of serum HBV DNA is a crucial component in the evaluation of patients with CHB infection and in the assessment of the efficacy of antiviral treatment[5]. The Phase 3 entecavir programme evaluated DNA suppression using highly sensitive Roche Amplicor assays, with a lower limit of quantification of 300 copies/mL. It is expected that the superior DNA suppression of entecavir to lamivudine in NA-naïve patients and the low rates of resistance to entecavir will result in long-term DNA suppression with lower rates of disease progression, cirrhosis and HCC.

Detection of elevated levels of liver aminotransferases in serum is regarded as a marker of liver damage. The value of ALT for a valuable parameter for assessing CHB activity is questionable since patients with normal ALT levels are still at risk for liver disease.

The patients entered into the Phase Three programme for entecavir reflect those that are to be treated in clinical practice. This includes adult patients with compensated CHB infection, active viral replication and liver inflammation. Both HBeAg-positive and HBeAg-negative patients, as well as NA-naïve and experienced patients, are also included.

The most common doses of entecavir administered in the studies (0.5 mg and 1.0 mg in NA-naïve and lamivudine-refractory patients, respectively) are the same as is recommended in the licensed indication. Accordingly, the results of the entecavir trials support the use of entecavir within its licensed indication.

In conclusion, for NA-naïve CHB patients, entecavir should be the preferred anti-viral therapy as it is more clinically effective in viral suppression with the lowest and near zero resistance rates. In NA-naïve HBeAg positive patients, entecavir is more clinically effective than other available first-line CHB therapies in viral suppression and is associated with the lowest resistance rates. In NA-naïve HBeAg negative patients, entecavir is more clinically effective than lamivudine and peginterferon and equivalent to telbivudine in viral suppression, and is associated with the lowest resistance rates among anti-viral therapies. In lamivudine-refractory patients, entecavir is a more clinically effective option compared with continuing lamivudine therapy in viral suppression.

6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic literature review was conducted to identify published economic models and information on costs, cost-effectiveness and QoL impact of CHB treatment, specifically entecavir, pegIFN, lamivudine, adefovir and telbivudine. Searches were conducted between September 5th and October 10th, 2007. No time limits were applied. Only English language publications were considered.

Databases searched

The following databases were searched using the search criteria specified below:

- PubMed (including MEDLINE and MEDLINE (R) In-Process
- EMBASE/MEDLINE (searched jointly on http://www.embase.com)
- CRD
- TRIP
- Cochrane library
- Internal databases

Additional searches conducted: NICE website, Scottish Medicines Consortium (SMC) website, Health Technology Asessment databases, EASL and AASLD databases, and a general web search using Google.

Search/inclusion criteria

- Full published papers reporting any of the following study designs: cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, QoL study (for QoL review) carried out in any country
- Condition: CHB only. Other types of hepatitis conditions were excluded.
- Treatment: entecavir, peginterferon, lamivudine, adefovir and telbivudine.
- Populations: adults with CHB. Studies in children and adolescents were excluded.
- Outcomes: cost estimates (including unit costs, resource utilisation), cost-effectiveness/utility measures, QoL, utility measures (the last two for the QoL review).

Complete search strategies are shown in Appendix 8.5.

Study selection

Studies were included in the systematic review if they described an economic evaluation quantifying both costs and benefits. However, no restrictions were placed on the type of economic evaluation or outcomes presented, such that cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses were all considered appropriate for inclusion. Review articles were excluded, although their bibliographies were examined for relevant references.

The SMC guidance on entecavir was added after the systematic review was conducted and is therefore not included in the number in Figure 6.1.

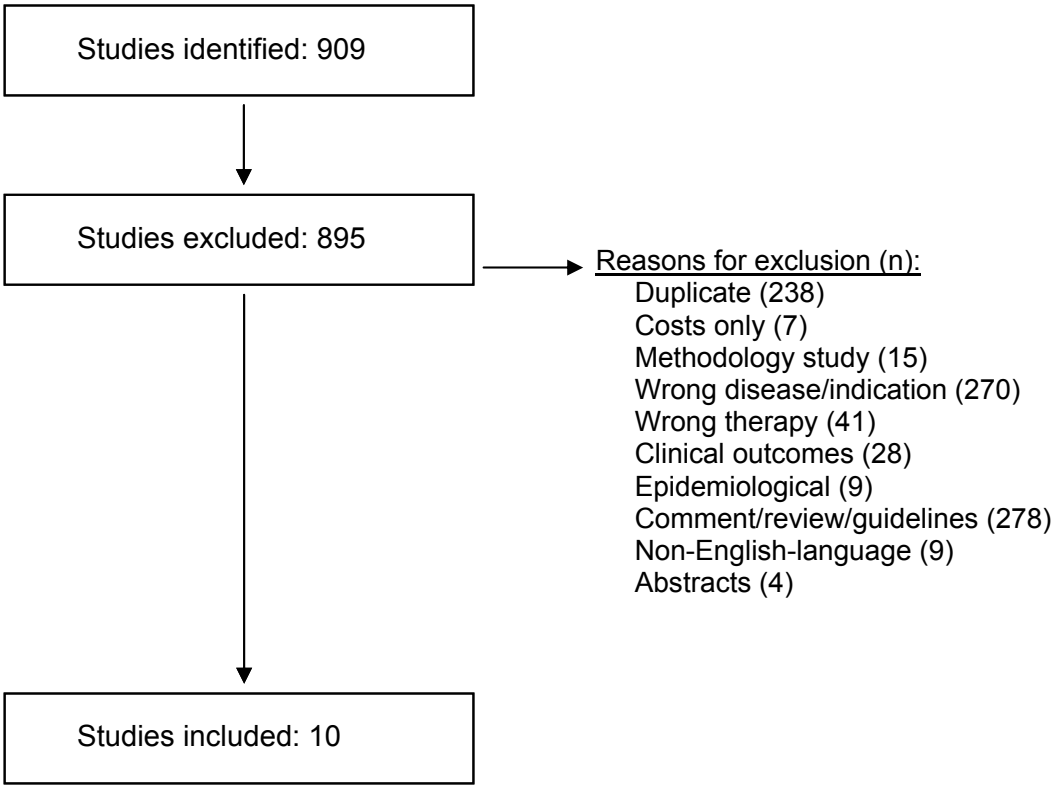


Figure 6.1: Economic evaluation search flow diagram

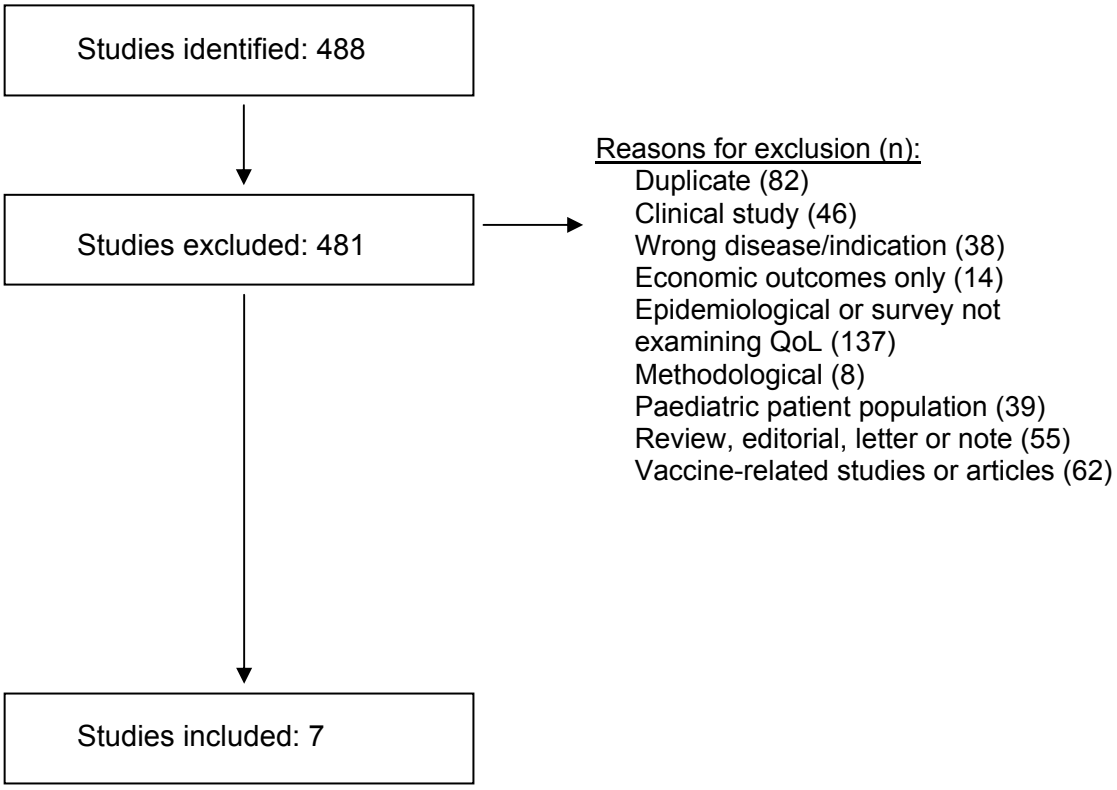


Figure 6.2: QoL search flow diagram

Data abstraction strategy

Ten economic analyses and seven QoL studies were included in the systematic review (Figures 6.1 and 6.2). Data were extracted into a prespecified table by one reviewer. A second reviewer conducted an independent data extraction and any discrepancies were discussed. Details extracted from all included studies are provided in Appendix 8.6 and 8.7. Key features of published studies as well as studies that include entecavir are summarised below.

6.1.2 Description of identified studies

As there are a large number of studies, only cost-effectiveness studies which were conducted in the UK setting, analyses relevant to decision making in the UK, or studies including entecavir as the comparator are summarised in Table 6.1. This table provides a summary of the type of evaluation, main results and applicability to UK decision making. All studies are detailed in Appendix 8.6.

Table 6.1: Economic evaluations of CHB treatments

Study	Treatment options	Type of evaluation	Main results
Kanwal et al, 2005[74]	A) No treatment B) IFNα C) Lamivudine D) Adefovir E) Adefovir salvage (i.e. switch) after lamivudine	Cost-utility analysis; Markov model	ICERs: - Strategy C and D are dominated by A, B and E - B vs. A: US$6,337 - E vs. B: US$8,446
Limitations - Excluded option to use lamivudine as a second-line therapy for patients who failed to seroconvert with IFNα. - Excluded option to add-on adefovir to lamivudine after lamivudine resistance; only considered switch to adefovir.			
Relevance to UK decision making – Relevant - Model acknowledges increasing prevalence of HBeAg-negative patients, as is the case in the UK. - Results are with different discount rates to current NICE reference case. - Adopts a US perspective and thus includes cost data that may not be applicable to the UK.			
Kanwal et al, 2006[75]	A) No treatment B) Lamivudine C) Adefovir D) Adefovir salvage after lamivudine E) Entecavir F) Entecavir salvage after lamivudine	Cost-utility analysis; Markov model	ICERs: - C vs. A: US$19,731 - E vs. C: US$25,626 - B, D and F were dominated by A, C and E. D dominated F.
Limitations - Several of the estimates were derived from studies of varying design, patient population, follow-up time and quality. - Study report is not explicit on patient type by HBeAg status (HBeAg-positive or –negative). - Excluded option to add-on adefovir to lamivudine after lamivudine resistance; only considered switches.			
Relevance to UK decision making – Limited - Included a narrow population, i.e. HBV patients with cirrhosis. 50% of patients had decompensated cirrhosis in the base case and baseline age was higher at 50 years. - Adopts a US perspective and thus includes cost data that may not be applicable to the UK. - Results are with different discount rates to current NICE reference case.			
Shepherd, 2006[55]	A) Best supportive care B) Interferon C) pegIFN D) Lamivudine E) Adefovir	Cost-utility analysis; Markov model	ICERs: - B vs. A: £5,944 - C vs. B: £6,119 - D vs. A: £3,685 - E vs. D: £16,569 ICERs (sequential treatment strategies): - £3,604 (IFN followed by lamivudine vs. IFN alone) - £11, 402 (IFN followed by lamivudine with adefovir salvage vs. IFN followed by lamivudine)
Limitations - Sequential treatment strategies are currently unsupported by evidence-based data. - Utility values included in the analysis were based on very little published evidence; no published data on the impact of antiviral treatment on HR-QoL.			

Relevance to UK decision making – Relevant - This model was produced by an independent UK-based academic group, on behalf of NICE, for the appraisal of pegIFN and adefovir. - The model appears to be well constructed and there is clear description of sources of information; however, the information is insufficient to determine the validity of the results. - There is a comprehensive sensitivity analysis. - Results are with different discount rates to the current NICE reference case.			
Veenstra et al, 2007[76]	A) PegIFN B) Lamivudine C) Adefovir salvage after lamivudine	Cost-utility analysis; Markov model	ICERs: - A vs. B: £10,400 - A vs. C: £6,100
Limitations - Included HBeAg-positive population only and does not fully represent the UK CHB population.			
Relevance to UK decision making – Relevant - There is a comprehensive sensitivity analysis. - Results are with different discount rates to the current NICE reference case.			
Entecavir SMC guidance	Entecavir versus lamivudine or adefovir	Cost-utility analysis; decision tree model	ICERs (NA-naïve patients)**:** - £12,000 HBeAg-positive - £15,000 HBeAg-negative ICERs (lamivudine-resistant patients)**:** - £9,000 for continuation with lamivudine - £17,000 for switch to adefovir
Limitations - Not enough detail about modelling approach for critical review			
Relevance to UK decision making – Relevant but not enough detail available - UK setting (Scotland)			
HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ICER: incremental cost-effectiveness ratio; NA: nucleo(s/t)ide analogue; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.			

6.1.3 Summary of the systematic review of economic analyses

Results of the published economic evaluations of CHB vary. Most studies report incremental cost-effectiveness ratios (ICERs) that fall within the generally acceptable cost-effectiveness ranges and are not consistently higher or lower than the ICERs produced by the SHTAC report for NICE technology appraisal 96[4 55]. However, direct comparison of the results of the published studies is not possible because the evaluations were very different in several respects:

- Different modelling approaches employed (decision trees and Markov models).
- Different time horizons (from 1 year to lifetime), comparator treatment (e.g. single treatment, multiple treatment sequences), outcome measures (e.g. cost per cirrhosis avoided, cost per additional seroconversion, QALY), source of preference weights, perspectives, discount rates, cost categories included/excluded.
- Studies were conducted in different countries, which may limit their applicability to the UK setting.
- A common limitation in all studies was the lack of long-term effectiveness data and clinical evidence on the use of sequential therapies.
- Despite the studies being generally of good quality there was no consensus of approach, most likely due to the difficulty of modelling chronic, long-term conditions with limited data.

6.2 De novo economic evaluation(s)

In the absence of UK-based economic evaluations of entecavir, a cost-effectiveness analysis was undertaken for this submission. This analysis draws upon many of the features used in previous models discussed in the systematic review.

6.2.1 Summary

Aim

The primary aim of this economic evaluation is to estimate the cost-effectiveness of entecavir as the first-line antiviral treatment for CHB in both HBeAg-positive and HBeAg-negative patients. The relevant comparator to entecavir in this patient group is lamivudine, which is the most widely used first-line antiviral treatment in the UK[30]. An analysis is also presented comparing entecavir with telbivudine, which is being considered in a parallel STA. Finally, as pegIFN is recommended by NICE as an initial option for CHB treatment[4], the cost-effectiveness of entecavir versus pegIFN is also estimated.

A secondary aim is to estimate the cost-effectiveness of entecavir in patients who have failed prior lamivudine therapy. The main comparator in this patient group is ADV/LVD combination therapy since it is the most widely used treatment strategy for patients who have failed lamivudine monotherapy[30]. This secondary analysis should be treated with caution due to lack of efficacy data for this comparison.

For all of the analyses undertaken, the perspective is the UK NHS and PSS and the cost-base year is 2006. This perspective reflects the NICE reference case for economic evaluation[77].

Methods

A Markov model was developed to estimate costs and outcomes (life-years and QALYs) of CHB patients from the beginning of their treatment to death[78]. Costs were taken from UK sources and publications identified in the systematic review. Utilities were determined from the UK-based participants in a multinational study[79].

Results

The results of the cost-effectiveness analysis suggest that entecavir is a cost-effective first-line antiviral therapy in HBeAg-negative and -positive patients with a cost per QALY versus lamivudine of £14,329 and £13,208 respectively. In the analysis against pegIFN, entecavir demonstrated cost-effectiveness with a cost per QALY of £8,403 and £7,511 as first-line CHB therapy in HBeAg-positive and -negative patients, respectively. In terms of cost-effectiveness in HBeAg-positive patients, telbivudine and entecavir have similar efficacy over a lifetime with a small difference in costs (telbivudine showing slightly lower cost of £187 versus entecavir over a lifetime). In HBeAg-negative patients, entecavir was cost-effective compared with telbivudine with a cost per QALY of £6,907.

The analysis in the lamivudine-refractory HBeAg positive patients suggests that entecavir dominates the LVD/ADV combination therapy. The results of this analysis should be treated with caution due to paucity of data in the HBeAg-positive lamivudine-refractory population.

6.2.2 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses,

frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

Entecavir is used in the model as per its licensed indication: for the treatment of CHB infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. Entecavir is taken orally with a recommended dose of 0.5 mg once daily for treatment-naïve patients and 1 mg once daily for patients who did not respond to prior lamivudine therapy.

As stated in the SmPC, the optimal duration of treatment with entecavir is unknown. For patients with HBeAg-positive disease and elevated ALT, the SPC states that treatment should be administered at least until HBeAg seroconversion or until HBsAg seroconversion or there is loss of efficacy. A 2-year treatment duration was assumed in the economic evaluation of entecavir in patients with HBeAg-positive disease as per the Phase 3 clinical trial detailed in the clinical section[56]. For patients with HBeAg-negative disease, long-term therapy is required in order to achieve sustained virological remission. A 5-year treatment duration was used as the base case, because recent evidence by Hadziyannis et al. suggests that virological remission can be maintained after discontinuation of successful long-term therapy of 4–5 years[80]. As clinical guidelines suggest that anti-viral treatment should continued indefinitely in HBeAg negative patients who do not achieve a sustained virological response)[15], lifetime treatment duration was explored in the scenario analysis.

6.2.3 Patients

6.2.3.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The modelled population is reflective of the licensed indication and the decision problem. The primary analysis evaluates the cost-effectiveness of entecavir as first line first-line antiviral treatment for adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation). HBeAg-positive patients are analysed separately from HBeAg-negative patients because these patient groups differ in the severity of disease, treatment required and evidence available. The characteristics of an average patient used in this base-case analysis are detailed in Table 6.2.

Table 6.2: Description of model cohorts.

	Patient population	
Parameter	**HbeAg-positive disease** (022[56])	**HbeAg-negative disease** (027[58])
Age (mean)	35 years	44 years
Baseline characteristics	HBV DNA positive HBeAg-positive Non-cirrhotic Elevated liver enzymes (ALT) Treatment-naïve: • no prior CHB therapy at least 6 months before study entry and; • no prior NA therapy (entecavir, lamivudine and telbivudine)	HBV DNA positive HBeAg-negative Non-cirrhotic Elevated liver enzymes (ALT) Treatment-naïve: • no prior CHB therapy at least 6 months before study entry and; • no prior NA therapy (entecavir, lamivudine and telbivudine)
ALT: alanine aminotransferase; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; NA: nucleo(s/t)ide analogue		

An analysis of patients who have failed LVD monotherapy was undertaken in the HBeAg positive patients, as ETV efficacy data is limited to this population only. ETV trial in the LVD refractory HBeAg positive population compared ETV switch to the continued use of LVD in this patient population and not to ADV/LVD combination therapy, which is the most widely used treatment strategy in the UK.[30] An indirect analysis was undertaken albeit using data from two small trials that compared ADV/LDV combination versus continued use of LVD in HBeAg-positive patients[81 82]. Given the data limitations in this comparison, the results should be treated with caution. The characteristics of an average patient are similar to the HBeAg-positive disease in Table 6.2 except that all patients were failing on lamivudine therapy (and were therefore not NA-naïve) at the time of study entry.

6.2.3.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

HBeAg-positive and HBeAg-negative patients were analysed separately because these patient populations differ in the severity of their disease, the treatment required and the evidence base available. Approximately 60% of CHB patients in the UK have HBeAg-negative disease[30], although this proportion is likely to be higher in immigrants who comprise 96% of new cases in the UK[6]. As discussed in Section 4.1.1, the HBeAg-negative form of the disease usually represents a later stage in the course of CHB infection. Patients tend to be both older and have more advanced liver disease than those who are HBeAg-positive. Therefore, some of the transition probabilities between health states for both patient groups can be expected to differ. Furthermore, treatment duration may differ in these patient groups, with HBeAg-negative patients requiring longer-term therapy so as to achieve sustained virological remission. Lastly, Phase 3 registration trials for entecavir were conducted separately in patients with HBeAg-positive and HBeAg-negative disease[56 58].

6.2.3.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

Based on the scope of this appraisal and the findings of the clinical review and NICE guidance[4], no obvious subgroups were excluded from this analysis.

6.2.3.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

To reflect the indication for entecavir, patients enter the economic evaluation at the time of starting antiviral therapy for the first time or at the time of nonresponse to lamivudine therapy and they exit at death. This is independent of treatment regimen.

6.2.4 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem.

As discussed in Section 4.1.3, two main classes of drug are used in the treatment of CHB: anti-virals, i.e. nucleos(t)ide analogues and interferons (IFNs). For treatment naïve patients, market research data show that lamivudine is the most widely used first-line CHB therapy in the UK with approximately 65% of CHB patients treated with lamivudine[30]. As such, lamivudine is the key comparator in this submission. Telbivudine, although not widely used in the UK, is specified in the scope of this appraisal and is being considered in a parallel STA. As such, telbivudine will also be considered as a comparator in this submission. NICE guidance recommends the use of pegIFN as an option for initial CHB therapy[4] and, as a result, pegIFN will be considered within the submission even though it is not widely used in the UK.

For patients who do not respond to lamivudine therapy, NICE guidance recommends the use of adefovir (either a switch to adefovir or add-on to existing lamivudine therapy)[4]. Market research data show that addition of adefovir to lamivudine is the current clinical practice within the UK with approximately 67% of patients being treated with adefovir receiving ADV/LVD combination therapy[30]. Therefore, ADV/LVD combination therapy is the key comparator in patients who do not respond to lamivudine therapy.

6.2.5 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective of the model is the NHS and PSS, reflecting the reference case[77]. This perspective potentially undervalues the therapeutic benefits and therefore the cost-effectiveness of entecavir, as patient benefits such as the ability to continue working, increased work productivity and reduced negative psychological and social symptoms due to CHB condition are excluded.

6.2.6 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The model was run for a lifetime horizon because CHB is a chronic and progressive disease and many health and economic outcomes accumulate over the course of an individual's life. As such, a lifetime horizon was appropriate given that the evaluation is concerned with treatments that seek to delay, and possibly avoid, sequelae that result in significant impact on patients' QoL and substantial excess mortality.

6.2.7 Framework

6.2.7.1 Description of the model type

Separate Markov state transition models were developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) by the Veritech Corporation for HBeAg-positive and HBeAg-negative disease groups[78]. As the original models projected treatment outcomes from the perspective of a US payer, they were adapted to reflect the UK treatment pathway and perspective. The structure of both models is similar to the model developed by SHTAC that was used in the 2006 NICE technology appraisal[55]. Each model estimates the incremental cost-utility of entecavir in comparison to the comparators specified in Section 6.2.4.

6.2.7.2 Schematics of the models

Schematics of the HBeAg-positive and HBeAg-negative disease models are presented below in Figures 6.3 and 6.4.

HBeAg positive model

In the HBeAg-positive disease model, 14 mutually exclusive health states were defined by patient clinical characteristics (Figure 6.3). A closed cohort of treatment-naïve patients (aged 35 years) who were HBV DNA-positive, non-cirrhotic and had elevated liver enzymes entered the model in the CHB state. These patients were treated for 2 years with entecavir, lamivudine or telbivudine. Patients treated with pegIFN were treated for 1 year, as recommended in the SmPC, and did not go on to other therapies in year 2 because patients continue to seroconvert post-treatment. For patients who developed resistance to antiviral agents, adefovir was added to their existing treatment.

During each subsequent cycle patients either remain in the health state they are in or move to a different health state, with movement being in the direction of the arrows. Patients could experience treatment-induced or spontaneous HBeAg seroconversion, spontaneous seroreversion or treatment relapse, and HBsAg loss. Patients could also develop antiviral drug resistance with or without a severe hepatic flare (defined as ALT >10×ULN). A key clinical event was the progression from CHB to compensated cirrhosis. Patients that developed compensated cirrhosis could then progress to decompensated cirrhosis and then require a liver transplant. HBeAg seroconverted patients could develop inactive cirrhosis, which was associated with a significantly lower risk of decompensation than compensated cirrhosis[83] [84] [85]. All patients in all states were assumed to be at risk for HCC except for those who experienced HBsAg loss or received a liver transplant.

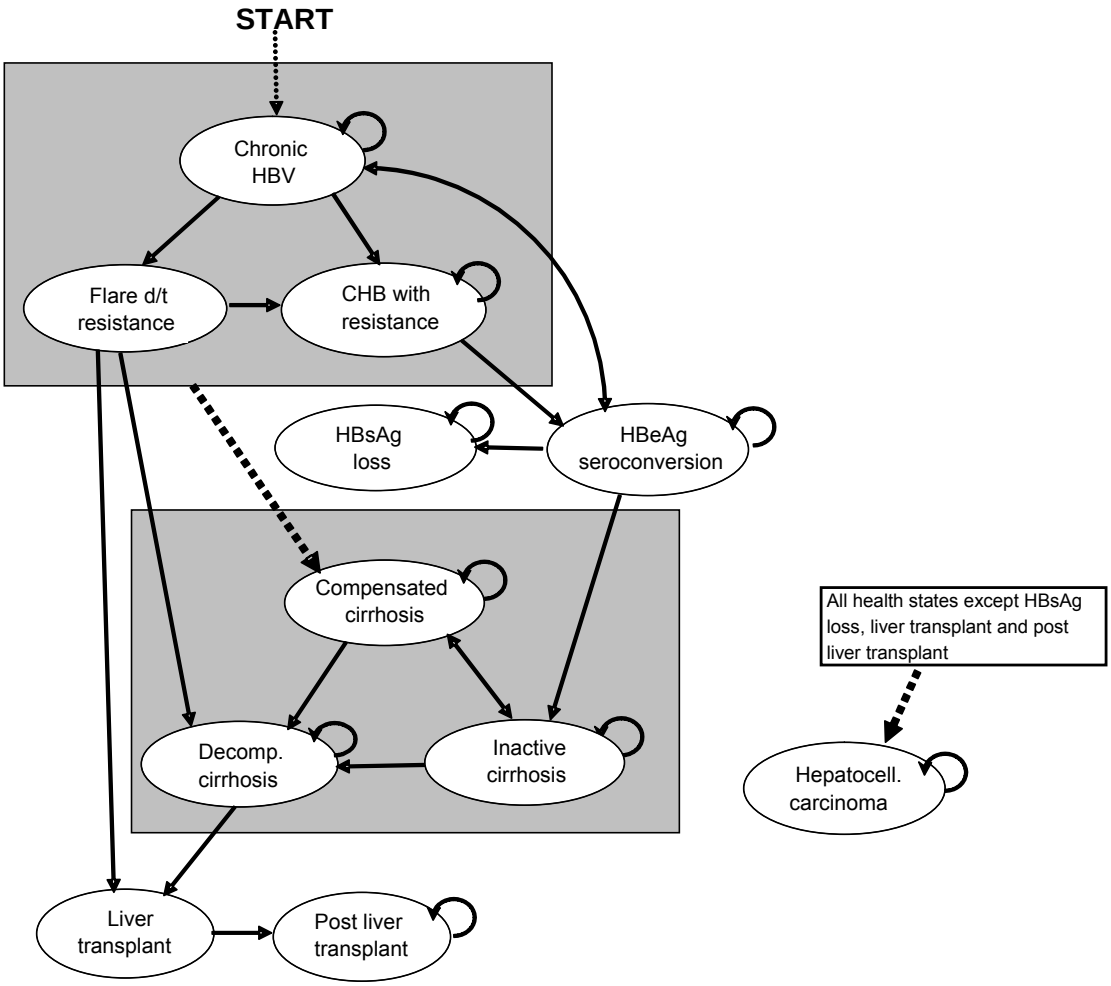


Figure 6.3: Schematic diagram for the HBeAg-positive disease model*

Legend: ——► Transition between individual health states

- - - - ► Transition between any health states in group to individual health state

*Not shown for clarity are health states for treated CHB, treatment-induced HBeAg seroconversion and death.

A version of the model represented in Figure 6.3 was used to perform a secondary analysis comparing entecavir with the ADV/LVD combination for patients who did not respond to prior lamivudine therapy. In this analysis, patients enter the model having failed lamivudine therapy. Treatment is again given for a maximum of 2 years. It is assumed that a third therapy would not be introduced for patients who develop resistance to antiviral agents.

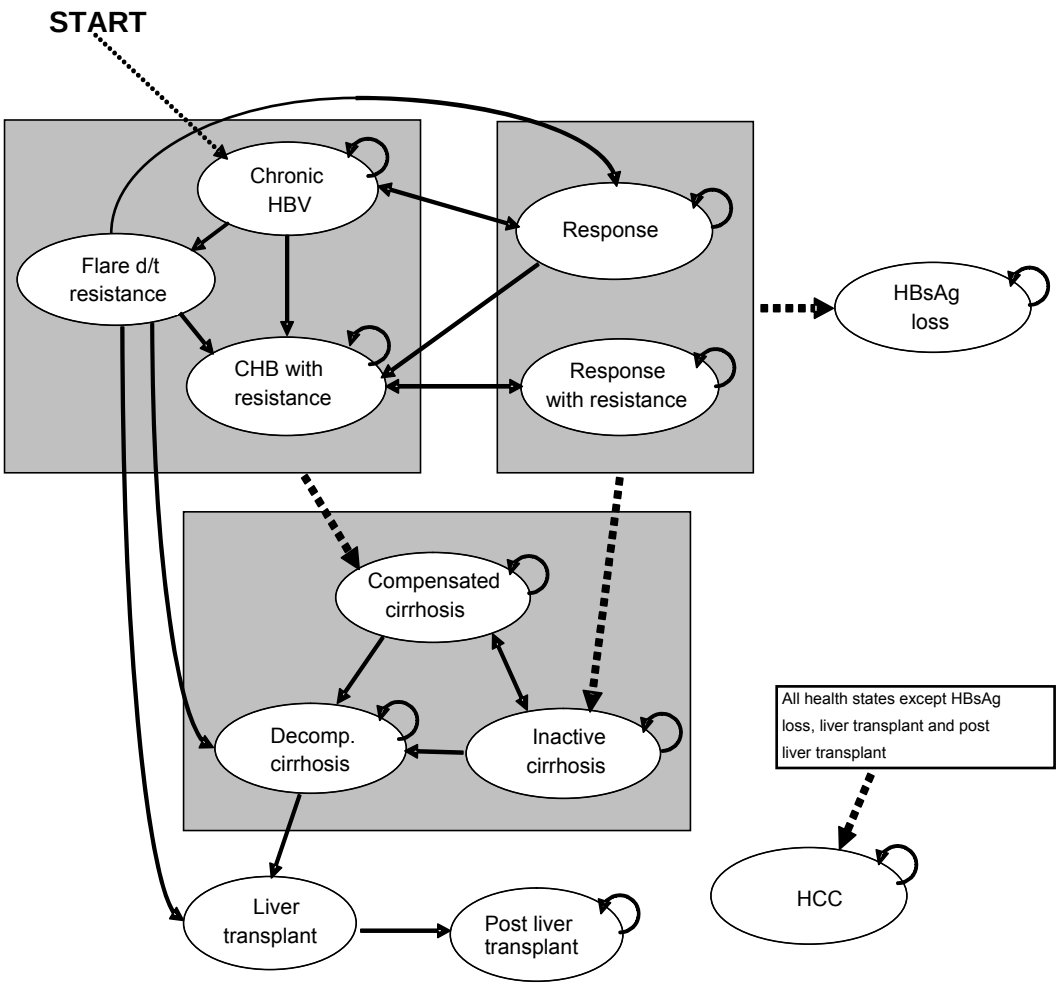


Figure 6.4: Schematic diagram for the HBeAg-negative disease model*

Legend: ——► Transition between individual health states

- - - - ► Transition between any health states in group to individual health state

* Not shown for clarity are health states for death and treated vs. untreated CHB and response.

HBeAg negative model

For the HBeAg-negative model, 15 mutually exclusive health states were defined by patient clinical characteristics (Figure 6.4). A closed cohort of treatment-naïve patients aged 44 years who were HBV DNA-positive, non-cirrhotic and had elevated liver enzymes entered the model in the CHB state. Treatment duration of 5 years was used to compare entecavir against the comparators lamivudine and telbivudine. For pegIFN, a fixed 1-year treatment was assumed as per the designated course of treatment, followed by a switch to long-term antiviral therapy (lamivudine first then followed by add-on adefovir when resistance developed). This was compared with 5-year treatment with entecavir. For patients who developed resistance to antiviral agents, adefovir was added to their existing treatment.

During each subsequent cycle, patients either remain in the health state they are in or move to a different health state, with movement being in the direction of the arrows. Patients could experience treatment-induced response (defined as undetectable HBV DNA by PCR assay), treatment relapse and HBsAg loss. Patients could also develop antiviral drug resistance with or without a severe hepatic flare (defined as ALT >10×ULN). As in the HBeAg-positive disease model, a key clinical event in disease progression was the transition from CHB to compensated cirrhosis, and patients entering this state could then progress to decompensated cirrhosis and

then on to require a liver transplant. Patients who achieved response, had a small risk of developing inactive cirrhosis, which was associated with a significantly lower risk of decompensation than compensated cirrhosis[83 84 85]. All patients were assumed to be at risk for HCC except for those who experienced HBsAg loss or received a liver transplant.

All-cause mortality, not specifically attributable to CHB-related complications, was modelled for both groups.

6.2.7.3 Lists of variables used in the model

Input parameters used in the models are divided into those that are independent of treatment (Table 6.3) and those that are treatment-specific (Tables 6.4 and 6.5). Most of the treatment-independent variables apply across the HBeAg-positive and -negative disease groups; where these values may only apply to one group, it is indicated in Table 6.3. Table 6.3 also indicates which transition probabilities are modified due to treatment effects listed in Tables 6.4 and 6.5.

For the majority of treatment-independent parameters listed in Table 6.3, the range was estimated on the basis that the events were Bernoulli in nature (and therefore a binomial distribution was assumed). The range for the remaining parameters was identified through a non-systematic literature review.

The range for the treatment-dependent parameters (in Tables 6.5 and 6.6) was derived from different distributions. For the values that were derived as part of the network meta-analyses, the range was calculated using standard errors which were based on a normal distribution. For the values that were not derived as part of the network meta-analysis, the range was calculated from data published in original sources for the base case values (the mean and sample size values reported in the sources were used to derive standard error estimates).

The range for utilities and health state costs were estimated by assuming a ±25% range around the central estimate for costs and a ±5% around the central estimate for utilities.

These ranges were used in the one-way sensitivitiy analyses (see Section 6.2.12).

Table 6.3: Treatment-independent annual disease progression probabilities*.

Parameter name	HBeAg status (+/–)	Value used	Range	Probabilities affected by treatment	References and comments
From CHB to:**					
HBeAg seroconversion	Positive	9	(6, 12)[a]	Yes	Mid-range from available estimates. Marcellin et al. 2003[86]; Yuen et al. 2003[87]; McMahon et al. 2001[88]; Lok et al. 1987[89]; Lai et al. 1998[90]; Dienstag et al. 1999[91]; Shepherd et al. 2006[55]
Response	Negative	0	-	Yes	Untreated patients do not respond.
Compensated cirrhosis	Positive	4.4	(0.4, 8.4)	Yes	Long-term study (Lin et al. 1999[92])
	Negative	9	(5.7, 12.3)	Yes	EASL[29]; Shepherd et al. 2006[55]
HCC	Both	0.5	(0.27, 0.73)	No	Wong et al. 1995[93]; DiBisceglie et al.[94]; Shepherd et al. 2006[55]
From flare to:					
DCC	Both	10	(8.13, 11.86)	No	Yuen et al. 2003[87]; Lok et al. 2003[71]
LT	Both	10	(8.13, 11.86)	No	Yuen et al. 2003[87]; Lok et al. 2003[71]
From no treatment to:					
HBsAg loss	Positive	1	(0.5, 1.5)	Yes [b]	
From HBeAg seroconversion to:					
CHB	Positive	1.8	(1.1, 2.5)	Yes [c]	Long-term observational study (McMahon et al. 2001[88])
HBsAg loss	Positive	1	(0.5, 1.5)	Yes [b]	
Inactive cirrhosis	Positive	0.1	(0, 0.46)	No	Long-term observational study (Hsu et al. 2002[83])
HCC	Positive	0.3	(0, 0.94)	No	
From response (defined as HBV DNA negativity by PCR assay) to:					
CHB (off-treatment)	Negative	70	(50, 90)	Yes[d]	Long-term adefovir study (Hadziyannis et al. 2006[80])
HBsAg loss	Negative	1	(0.5, 1.5)	No	Long-term observational study by (McMahon et al. 2001[88])
Inactive cirrhosis	Negative	0.1	(0, 0.46)	No	Long-term observational study by (Hsu et al. 2002[83])
HCC	Negative	0.3	(0, 0.94)	No	Hsu et al. 2002[83]; Kim et al. 2004[95]
From CC to:					
Inactive cirrhosis	Positive	9	(6, 12) [a]	No	Assumed to be the same as baseline HBeAg seroconversion rate
	Negative	0	–	No	Assumed to be the same as baseline response rate, i.e. 0%
DCC	Both	5	(2.52, 7.48)	No	Crowley et al. 2002[96]; Lavanchy et al. 2004[11]; Fattovich et al. 1991[97]; 1997[98]; Shepherd et al. 2006[55]
HCC	Both	2.5	(0.72, 4.28)	No	Wong et al. 1995[93]; DiBisceglie et al.[94]; Crowley et al. 2002[96]; Shepherd et al. 2006[55]
From inactive cirrhosis to:					
CC	Positive	4.4	(0.4, 8.4)	No	Assumed to be the same as from CHB to CC
	Negative	9	(6, 12) [a]	No	
DCC	Both	0.8	(0, 1.81)	No	Fattovich et al. 2002[84]
HCC	Both	2.5	(0.72, 4.28)	No	Assumed to be the same as from CC to HCC
From DCC to:					
HCC	Both	2.5	(0.72, 4.28)	No	Assumed to be the same as from CC to HCC
LT	Both	3	(2.42, 3.57)	No	Bennett et al. [99]; Shepherd et al. 2004[100]; Shepherd et al. 2006[55]
Death	Both	22	(17.3, 26.7)	No	Fattovich et al. 1997[101]
From HCC to:					
Death	Both	23.3	(13.3, 33.3)	No	Bolondi et al. 2001[102]
From LT to:					
Death	Both	13.0	(11.9, 14.1)	No	Kim et al. 2004[95]
From Post-LT to:					
Death	Both	2.5	(1.98, 3.02)	No	Kim et al. 2004[95]
From all other states to:					
Death	Both	Age-dependent	– [e]	No	Office for National Statistics[103]

*Annual disease progression probabilities for resistance and flare states are the same as for progression rates from the CHB state; **CHB to flare is a derived probability: (Probability of developing treatment resistance)×(Proportion of flares due to resistance i.e. 2% from Lok et al.[71]).

[a] Range was based on the lowest and highest estimates obtained from the literature review. [b]Treatment effects apply in the year after HBeAg seroconversion (CSR 022[57]); [c] A higher rate for reversion to CHB applies in the year immediately following HBeAg seroconversion with the exact value of this reversion being treatment-dependent; [d] Treatment effects apply while patients are on therapy only;
[e] Based on population statistics and not sample data;
CC: compensated cirrhosis; CHB: chronic hepatitis B; CSR: clinical study report; DCC: decompensated cirrhosis; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; LT: liver transplant; PCR: polymerase chain reaction.

Table 6.4: Treatment-specific model parameters for HBeAg-positive disease.

Treatment	CHB to HBeAg seroconversion in years 1 and 2[a]	HBeAg seroconversion to CHB[b]	Annual resistance years 1 and 2[c]	Relative risk of cirrhosis for CHB patients (who do achieve HBeAg seroconversion)[d]	Source
Treatment-naïve patients					
Entecavir	Yr1: 18.3%[†] Yr2: 10.4%[†]	18%[57]	Yr1: 0.2%[67] Yr2: 0.2%[67]	Yr1: 0.13[† 57 104] Yr2+: 1	Network meta-analysis[†]; Iloeje et al. 2006[104]; CSR[57 67]
Lamivudine	Yr1: 18.3%[†] Yr2: 7.2%[†]	27%[57]	Yr1: 23.0%[89] Yr2: 23.0%[89]	Yr1: 0.51[† 57 104] Yr2+: 1	Network meta analysis[†]; Chang et al. 2006[56]; Lok et al. 1987[89]; Iloeje et al. 2006[104]; CSR[57]
PegIFNα-2a	Yr1: 24.5%[†] Yr2: 8.3%[19]	18%[19]	Yr1: 0%[19] Yr2: 0%[19]	Yr1: 0.98[† 19 104] Yr2+: 1	Network meta-analysis[†]; Lau et al. 2005[19]; Iloeje et al. 2006[104]
Telbivudine	Yr1: 19.7%[†] Yr2: 11.7%[†]	20%[72]	Yr1: 3%[73] Yr2: 19.6%[72]	Yr1: 0.19[† 104 72] Yr2+: 1	Network meta-analysis[†]; Iloeje et al. 2006[104]; Han et al. 2007[72] Lai et al 2005[73]
Adefovir salvage therapy	Yr1: –[e] Yr2: 7%[81 82]	21%[f]	0%[g]	Yr1: –[e] Yr2+: 1	Peters et al. 2004[81]; Perrillo et al. 2004[82]
Lamivudine-refractory patients					
Entecavir	Yr1: 8%[63] Yr2: 8.7%[63]	[redacted]	Yr1: 1%[67] Yr2: 9.3%[67]	Yr1: 0.17[63] Yr2+: 1	CSR[63 67]; Iloeje et al. 2006[104]
ADV/LVD	Yr1: 7%[81 82] Yr2: 7%[h]	[redacted]	Yr1: 7.4%[54] Yr2: 7.4%[54]	Yr1: 0.55[83 104] Yr2+: 1	Peters et al. 2004[81]; Perrillo et al. 2004[82] Iloeje et al. 2006[104]; Buti et al. 2001[54]

[†] Data extracted from the network meta-analysis. Full results of this are available in Section 5.6.

[a] Year 2 rates HBeAg seroconversion rates were derived by: [(cumulative rates of HBeAg seroconverison in year 2 – year 1 rates of HBeAg seroconversion)/proportion of patients who go on to year 2]

[b] HBeAg seroreversion to CHB was based on trial data that reported response rates post 6 months after treatment. These rates were assumed to hold for the entire year.

[c] Annual resistance rates were derived by: Entecavir – conversion of 4-year rate of approx 1 % to equivalent annual probability (see section 6.2.12), Telbivudine – same method as used to generate seroconversion in year 2 (see footnote b). Lamivudine – was based on information presented in Lok et al[105]

[d] Results from a recent large cohort study (REVEAL–HBV) study by Iloeje et al.[104] was utilised in combination with viral suppression data from the network meta-analysis and clinical trials. Details are provided in Section 6.2.7. The risk is presented as relative risk to baseline cirrhosis risk of 4.4% (see Table 6.3). In year 2, all patients revert to baseline risk of 4.4% or relative risk of 1 compared to baseline.

[e] Salvage therapy is added in year 2

[f] As there are no data on HBeAg seroreversion to CHB for ADV/LVD combination in this population, a weighted average of the rates (for the other four therapies in the table) was used to estimate HBeAg seroconversion to CHB for adefovir.

[g] Resistance to salvage therapy was assumed to be 0% and third therapy was not considered.

[h] Due to the lack of data, rate was assumed similar to year 1.

[i] Due to the lack of data on HBeAg seroconversion durability for ADV/LVD combination, rate was assumed to be similar to entecavir.

Table 6.5: Treatment-specific model parameters for HBeAg-negative disease.

Treatment	CHB to response in year 1 [a]	CHB to response in years 2–5 [b]	Resistance in year 1 [c]	Resistance in years 2–5 [c]	Source
Entecavir	90.5%†	35.8%†	0.2%[67]	0.2%[67]	Network meta-analysis†; CSR[59 67]
Lamivudine	71.5%†	19.6%†	11%[106]	28%[106]	Network meta-analysis†; Di Marco et al.[106]
pegIFNα-2a	61%†	Assumed to be equal to lamivudine rates [d]	0%[20]	Assumed to be equal to lamivudine rates [d]	Network meta-analysis†; Marcellin et al.[20]; Di Marco et al[106]; Lai et al[58]
Telbivudine	87.9%†	32.2%†	2%[73]	7%[72]	Network meta-analysis†; Han et al [72]; Lai et al 2005[73]
Adefovir salvage therapy	– [e]	60% [50 51 116]	– [e]	0 [f]	Lampertico et al. [50];Rapti et al[51]; Vassiliadis et al[116]

[a] Response is defined by HBV DNA negativity by PCR assay (<300/400 copies/mL).
[b] Year 2 response rates were derived by: [(cumulative rates of undetectable viral load in year 2–year 1 rates of achieving undetectable viral load/proportion of patients who go on to year 2]. Due to lack of data, year 2 rates were assumed to hold for years 3–5.
[c] Annual resistance rates for entecavir and telbivudine were calculated as per footnote c in Table 6.4 (for lamivudine resistance, rates were taken from a publication by Di Marco et al.[106]). For entecavir, year 4 resistance rate was assumed to hold for year 5. For lamivudine and telbivudine, year 2 resistance rates were assumed to hold for years 3-5.
[d] It is assumed that patients who move on to lamivudine (followed by addition of adefovir when resistance develops) after the designated treatment duration of 1 year of pegIFN therapy have similar response and resistance rates as patients starting anew on lamivudine therapy
[e] Salvage therapy does not begin until year 2
[f] Resistance to salvage therapy was assumed to be 0% and a third therapy was not considered.

6.2.7.4 Model assumptions

Table 6.6: Assumptions used in the construction of the HBeAg-positive disease model

Assumption	Justification
Treatment duration is 2 years for all interventions except pegIFNα-2a where treatment duration is 1 year (as per designated duration).	Reflects available clinical trial data for entecavir, lamivudine, telbivudine and pegIFN[19 57 73 72]
48- and 96-week trial data is assumed to be applicable to 1-year and 2-year data in the model irrespective of treatment.	As the difference between the timepoints is small (i.e. 48 weeks vs. 52 weeks) this was thought not to have a significant impact on the results.
Patients on antivirals who did not achieve HBeAg seroconversion at the end of year 1 were continued on therapy in year 2.	This gives patients who do not seroconvert at the end of year 1 and remain in the CHB state one more year of chance to seroconvert.
Patients on antivirals who achieved HBeAg seroconversion at the end of year 1 were discontinued from therapy in year 2.	Reflects available clinical trial data for entecavir.
Patients who developed antiviral drug resistance had adefovir added to their existing treatment regimen, with the assumption that patients who developed resistance in year 2 received combination salvage therapy, i.e. (existing plus ADV salvage) in year 3.	Reflects UK market research evidence which demonstrates that the ADV/LVD combination is the most widely used treatment for lamivudine-refractory patients[30]. There is no evidence on efficacy of adding adefovir to either entecavir or telbivudine. However, AASLD guidelines recommend addition of adefovir when entecavir/telbivudine resistance develops[5].
Costs of salvage therapy added in year 2 and continued in year 3 are included in the model but the transition probabilities revert to the baseline rates.	The only efficacy data for ADV/LVD in this patient group is based on two small studies[81 82] and the seroconversion rates are lower than the baseline transition probabilities (8% and 6%). This assumption ensures that the efficacy of salvage therapy is not biased downwards.
Response to salvage therapy was assumed to be the same for all interventions under consideration.	Assumed to be same due to the lack of data on rescue therapies.
Patients who did not seroconvert but achieved complete viral suppression (undetectable HBV DNA by PCR) in year 1 and continued therapy had a reduced risk of cirrhosis in year 2.	Reflects the findings presented in the REVEAL study by Iloeje et al. where the risk of cirrhosis was found to decrease significantly with decreasing HBV DNA levels, independently of HBeAg status and serum ALT level[104]. The cirrhosis risk estimate of 2.2% obtained for lamivuidine using REVEAL study (in combination with viral suppression data from entecavir trial[107]) was in line with the estimate of 2% used by Shepherd et al.[55], validating the use of REVEAL data for calculating cirrhosis risk.
Relationship between risk of cirrhosis and HBV DNA levels observed in the REVEAL study in untreated patients is assumed to be applicable for treated patients.	Without data to suggest otherwises, it is reasonable to assume risk of cirrhosis is reduced whilst viral suppression is maintained and this assumption is consistent with clinical expert opinion.
Treatment specific likelihoods of seroconversion, resistance and seroreversion only apply when individuals are on therapy; post-treatment patients revert back to baseline values.	There are no data to suggest that post-treatment patients have different underlying disease progression rates.
Individuals who have HCC cannot go on to receive a liver transplant.	Same assumption as that in the SHTAC report that informed NICE TA96[4 55].

AASLD: American Association for the Study of Liver Diseases; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; pegIFN: pegylated interferon; PCR: polymerase chain reaction; REVEAL: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer; SHTAC: Southampton Health Technology Assessment Centre.

Table 6.7: Assumptions used in the construction of the HBeAg-negative disease model

Assumption	Justification
Treatment duration is 5 years for all interventions except pegIFNα-2a where treatment duration is 1 year (as per designated duration).	HBeAg-negative patients require longer-term therapy[5]. Recent evidence by Hadziyannis et al. suggests that virological remission can be maintained after discontinuation of successful long-term therapy of 4–5 years[80]. Lifetime treatment duration was explored in the scenario analysis.
48- and 96-week trial data is assumed to be applicable to 1-year and 2-year data in the model irrespective of treatment.	As the difference between the timepoints is small (i.e. 48 weeks vs 52 weeks) this was thought not to have a significant impact on the results.
Patients who achieved treatment response, as defined by HBV DNA negativity by PCR assay, had decreased risks of cirrhosis and HCC.	In line with findings from previous assessment and large cohort studies[40 55 74 104].
Patients who developed antiviral drug resistance had adefovir added to their treatment regimen.	Reflects UK market research evidence which demonstrates that the ADV/LVD combination is the most widely used treatment for lamivudine-refractory patients[30]. There is no evidence on efficacy of combination therapy for entecavir and telbivudine, i.e. entecavir/telbivudine plus adefovir. However, AASLD guidelines recommend addition of adefovir when entecavir/telbivudine resistance develops[5].
Response to salvage therapy was assumed to be the same for all interventions under consideration.	Assumed to be same due to the lack of data on rescue therapies.
Patients who failed to achieve viral suppression with pegIFN therapy were switched to antiviral therapy in year 2 (lamivudine first followed by add-on adefovir when resistance developed).	Unlike HBeAg-positive patients, who continue to seroconvert in year 2 after coming off pegIFN treatment, HBeAg-negative patients who do not respond to treatment in year 1 do not achieve response in year 2. As such, a wait-and-see approach as in the positive model is not feasible, and antiviral therapy is given in year 2.
Patients who achieved viral suppression with pegIFN therapy at the end of year 1 were all switched to antiviral therapy in year 3 (lamivudine first followed by add-on adefovir when resistance developed).	Only 19% of the 63% of patients who achieved viral suppression with pegIFN therapy at the end of year 1 maintained response at 72 weeks[19]. As the risk of relapse is substantial, it was assumed that all patients go on antiviral therapy in year 3.
The treatment effect of lamivudine following pegIFN therapy was assumed to be similar to lamivudine therapy alone.	Assumed due to lack of clinical trial evidence on efficacy of sequential therapy, i.e. lamivudine therapy following pegIFN failure.
Probability of response in year 3+ is assumed equal to year 2.	Assumed due to lack of data.
Treatment durability for all antiviral therapies was estimated to be 30% after a minimum of 5 years.	Based on findings from a small follow-up study of patients treated with adefovir for 5 years which found that 1/3 patients became HBV DNA negative at follow-up[80].
Patients that relapsed once off treatment had the same disease progression rates as untreated patients	Based on study findings[40 80 104].
Individuals who have HCC cannot go on to receive a liver transplant	Same assumption as in the SHTAC report that informed NICE TA96[4 55].
AASLD: American Association for the Study of Liver Diseases; CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; pegIFN: pegylated interferon; PCR: polymerase chain reaction; SHTAC: Southampton Health Technology Assessment Centre.	

6.2.7.5 Why was this particular type of model used?

As discussed in Section 6.1, two approaches have been used to estimate the cost-effectiveness of CHB treatments: decision trees and Markov models (cohort simulation)[78]. The Markov framework was considered most appropriate for this submission, as it has been previously applied for a health technology assessment

undertaken by NICE to assess technologies for the treatment of CHB[55]. The Markov framework allows a realistic representation of the disease and avoids over-simplifications while remaining transparent.

6.2.7.6 Justification for the chosen structure

What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The approach adopted for this submission reflects previous evaluations including the previous health technology assessment undertaken by NICE[55], as well as the available data.

The ultimate goals of therapy are to decrease the incidence of cirrhosis, end-stage liver disease, HCC and liver-related mortality[5]. Evidence has emerged to establish viral load as an important predictor of CHB disease progression. Iloeje et al. conducted a population-based prospective cohort study of 3,582 untreated HBV-infected patients – the largest natural history study of CHB patients to date – where the risk of cirrhosis was found to decrease significantly with decreasing HBV DNA levels, independently of HBeAg status and serum ALT level[104]. As a result, sustained reduction in viral load is gaining importance as a key therapeutic endpoint employed in clinical trials.

For HBeAg-positive patients, viral load reduction to undetectable DNA levels facilitates HBeAg seroconversion, which is used to monitor patient response and determine treatment discontinuation[15]. Thus, the HBeAg-positive disease model uses HBeAg seroconversion as well as sustained HBV DNA suppression to represent the course of CHB.

The HBeAg-negative disease is a variant form of viral infection without the secretion of HBeAg and therefore HBeAg seroconversion is not relevant. As such, the HBeAg-negative disease model uses sustained HBV DNA suppression to represent the course of CHB.

CHB trials also consider other response measures such as histological improvement and ALT normalisation. Histological improvement, used to assess improvements in necroinflammation and fibrosis, is an invasive procedure and may be prone to sampling error and intra-observer variability. Mommeja-Marin et al. showed that liver histological damage was the consequence of HBV viral replication[45]. This, coupled with increasing evidence on disease regression due to active suppression of viral replication, is shifting the earlier emphasis on improvement in liver histology to reduction in viral load. ALT normalisation is used as an indicator of liver inflammation, but its value as a reliable parameter for assessing CHB disease activity and as an indicator for treatment is questionable, since patients with normal ALT levels are still at risk of liver disease[14 5]. For these reasons, these other response measures were not considered relevant to this analysis.

6.2.7.7 Sources of information

What were the sources of information used to develop and inform the structure of the model?
The model structure is in line with the model developed by Shepherd et al[55] and reflects expert opinion from clinicians, statisticians, decision modellers and health economists.

6.2.7.8 Relevance of the model to the decision problem

Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?
The model structure reflects all essential features of CHB that are relevant to the decision problem.

6.2.7.9 Cycle length

For discrete time models, what was the model's cycle length and why was the length chosen? Does the length reflect a minimum time over which the pathology of symptoms of a disease could differ? If not, why not?
A 1-year cycle length was used for both models. This cycle length was deemed sufficient to capture key events in the patient pathway given the comparatively slow rate of progression of CHB disease, reflects available data and is in line with the previous HTA conducted by NICE in CHB[55].

6.2.7.10 Half-cycle correction

Was a half cycle correction used in the model? If not, why not?
A half cycle correction was applied (to both costs and QALYs) in each model cycle.

6.2.7.11 Extrapolation of costs and clinical outcomes

Are costs and clinical outcomes extrapolated beyond the trial follow up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term differences between the technology and its comparator(s)?
For the HBeAg-positive disease model, a 2-year treatment duration was used. Where possible, 2-year data were used to inform all parameters, and where none was available, trial information from studies with different follow-up durations (e.g. 48, 72 or 96 weeks) were extrapolated to the relevant endpoints by using probability/rate conversions using standard methodology[108]. As such, clinical outcomes were not extrapolated beyond the trial follow-up period for HBeAg-positive disease patients unless data was unavailable.

For HBeAg-negative disease model, the maximum treatment duration was set to be 5 years. As such, clinical outcomes were extrapolated beyond trial follow-up and assumptions were made concerning long-term HBV DNA suppression and drug resistance (see Tables 6.5 and 6.7). The key assumption made for both entecavir and its comparators was that the calculated response rates for year 2 would hold for all subsequent treatment years (except for resistance data, as 4-year data for entecavir is available).

6.2.8 Clinical evidence

6.2.8.1 Estimating the baseline risk of disease progression

How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Baseline rates of disease progression were derived from a non-systematic review of the literature as shown in Table 6.3. These values represent the underlying transition probabilities associated with no drug treatment. For the evaluation of each of the anti-viral drug therapies, the natural history transition probabilities were replaced with treatment effects as shown in Tables 6.4 and 6.5.

The baseline rates of disease progression in each of the models are discussed in detail below.

HBeAg-positive disease model

The risk of progression to cirrhosis from the CHB health state is an important parameter in the model, but difficult to evaluate because many of the longitudinal studies identified did not serially evaluate HBeAg status and may therefore underestimate the risk, due to a significant proportion of patients seroconverting during the follow-up period. In a prospective study of 509 HBeAg-positive CHB patients followed up for a mean period of 35 months, Liaw et al. reported an annual risk of cirrhosis of 2.4%[109]. In contrast, in a randomised trial evaluating the efficacy of IFN treatment, Lin et al. followed patients for a mean of 6.5 years and found that the annual risk of cirrhosis in the placebo group was 4.4%[92]. Earlier cost-effectiveness models used estimates of up to 12% per year[110 111]. More recent cost-effectiveness analyses, however, have used annual rates of 3.2–5.0%[55 112 113]. The annual risk of cirrhosis was taken from the Lin et al. study because this longer-term study gathered more information than shorter studies and can therefore provide a more reliable estimate[92].

Another important parameter in the model is the baseline probability of spontaneous seroconversion. In a long-term study of 1,536 Alaskan natives (median follow-up 12.6 years) McMahon et al. found that 541/641 (84%) patients who were initially HBeAg-positive seroconverted at some point during the study[88]. This corresponds to a rate of 13% per year. In an earlier study, Lok et al. estimated an annual rate of 12%[89]. In contrast, three randomised trials have found 1-year rates of 4–6%[86 90 91] in untreated patients, and previously published economic models have used values ranging from 6.9–12%[55 74 93 96]. Based on this range of estimates, a baseline rate of 9% per annum was chosen as the midpoint value and used in the base-case analysis. This is consistent with estimates used by Shepherd et al. to inform NICE TA96[4 55].

The risk of mortality for patients remaining in the cirrhosis state without progression to decompensation or HCC was assumed equal to the general age-specific UK all-cause mortality rates[103]. The model developed by Shepherd at al. assumed a significantly increased risk of excess mortality among cirrhotic patients[55]. The clinical events that lead to premature death for these patients such as HCC and decompensation are, however, already captured in the current models for this submission.

The annual probability of liver transplantation of 3% for a decompensated patient was based on the estimate used by Shepherd et al[55]. It was assumed that patients with HCC did not receive a liver transplant[55].

The remaining parameter estimates for disease progression reported in Table 6.3 are generally consistent with those used in previously published cost-effectiveness analyses[55 74 93 96].

HBeAg-negative disease model

The risk of progression to cirrhosis from CHB state is an important parameter but is difficult to evaluate because of the lack of data in this patient group. The cost-effectiveness model developed by Shepherd et al.[55] used an annual risk of 9% based on EASL consensus estimates[29]. In this submission an annual rate of 9% was used in the base case analysis as per Shepherd et al.[55].

As in the HBeAg-positive disease model, the mortality risk associated with patients remaining in the cirrhosis state without progression to decompensation or HCC was assumed to be equal to the general population in the UK; the estimated annual probability of liver transplantation for a decompensated patient was 3% based on the estimate used by Shepherd et al.[55] and it was assumed that no patients were transplanted due to HCC.

Untreated patients were assumed not to experience spontaneous response (as defined by HBV DNA negativity by PCR assay), in contrast to assumptions made by Kanwal et al.[74] (1.6%) and Shepherd et al.[55] (14% with 2.9% spontaneous relapse).

The remaining parameter estimates for disease progression reported in Table 6.3 are again consistent with those used in previously published cost-effectiveness analyses[55 74 93 96].

6.2.8.2 How were the relative risks of disease progression estimated?

The natural history transition probabilities were replaced with the different treatment effects as shown in Table 6.4 and Table 6.5. Treatment-specific likelihoods of seroconversion, resistance and seroreversion only apply when individuals are on therapy; post-treatment patients revert back to baseline values. The principle drivers of treatment effects were HBV DNA suppression, HBeAg seroconversion and resistance rates as these factors influence the probability of developing progressive liver disease. A network meta-analysis to estimate these treatment effects was undertaken (resistance was not included in the network meta-analysis as data come from non-RCT and the patient populations were too heterogeneous) in order to capture information from as wide an evidence base as possible, and to incorporate both direct and indirect comparisons between the included interventions (full details reported in Appendix 8.4). Entecavir was used as the baseline comparator, with all treatment effects being calculated relative to this intervention. Baseline results for entecavir were calculated as log odds (i.e. the odds of a particular event happening were reported on a log scale), and treatment effects were reported as log-odds ratios. These values were combined as necessary to generate odds, and subsequently transition probabilities using standard formulae[114].

HBeAg-positive model: treatment-naïve patients

In this model, the key parameters used to assess treatment effect is the proportion of individuals who achieve HBeAg seroconversion, undetectable HBV DNA levels (defined as <300 or 400 copies/mL) and drug resistance. Table 6.4 provides detailed information on the clinical parameters.

CHB to seroconversion: The probability of seroconversion for all interventions in years 1 and 2 was derived as part of the network meta-analysis (see Section 5.6).

For pegIFN, 1 year of treatment is associated with 2 years of effect as patients continue to serconvert after coming off treatment. Lau et al. report that a cumulative percentage of 32% of patients achieved HBeAg seroconversion at 24 weeks post-therapy[19].

Resistance to seroconversion: In year 2, the percentage of patients who seroconvert on salvage therapy (7%) and remain in the seroconversion state (79%) is estimated to be 5.5%. The HBeAg seroconversion rate for lamivudine-resistant patients receiving ADV/LVD combination therapy was chosen from Peters et al.[81] and Perrillo et al.[82] who report 1-year seroconversion rates for combination therapy as 6% and 8% respectively. Due to lack of data in sequential treatment for entecavir and telbivudine, 7% value was assumed to hold for all interventions (when adefovir is added to existing therapy due to emergence of resistance on the first therapy). The estimate of percentage of patients remaining in the seroconversion state (79%) is the inverse of the average percentage (21%) of patients relapsing (i.e. moving from the seroconversion state to CHB) for all therapies (see Table 6.4).

Seroconversion to CHB: The probability of sero-reverting in year 2 and 3 for entecavir (18%) was taken from 022 trial[56] for all comparisons except versus ADV/LVD combination therapy, for which the 026 trial[62] was used because it was a more appropriate patient population ([redacted] in a lamivudine-refractory patients). Probabilities for lamivudine (27%) were obtained from Lok et al[71], for telbivudine (20%) from Han et al[72], for pegIFN (18%) from Marcellin et al[20], and for ADV/LVD the probability was assumed to be the same as for entecavir ([redacted]). These were 6 months post-treatment follow-up rates, which were assumed to hold for the entire year.

CHB to resistance: Long-term data show that the cumulative probability of resistance over 4 years of therapy is approximately 1% for entecavir (see Section 5.8.5). To avoid introducing any bias into the model that might favour entecavir, the annual probability of resistance to entecavir was estimated to be 0.2%. For lamivudine, the annual probability of resistance was estimated to be 23%, which was taken from an open-label study by Lok et al, who reported that lamivudine resistance in years 1 and 2 were 23% and 46%, respectively[71].

Resistance values for telbivudine were taken from the GLOBE study, with Lai et al. reporting 1-year resistance rates of 3%[73] and Han et al[72] reporting cumulative resistance rates at year 2 of 22% The annual probability of telbivudine resistance was estimated to be 3% in year 1 and 19.6% in year 2.

Resistance to adefovir salvage therapy was assumed to be 0% for all treatments.

CHB to cirrhosis (cirrhosis risk reduction): Increasing evidence is emerging to establish viral load as a predictor of CHB disease progression. The REVEAL–HBV study – a 13-year prospective, population-based cohort study involving 3653 Taiwanese patients with CHB infection, the largest natural history study of CHB patients to date – demonstrated that the progression to cirrhosis in CHB patients is strongly correlated with the level of circulating virus and the risk for cirrhosis was found to decrease significantly with decreasing HBV DNA levels, independently of HBeAg status and serum ALT level[40]. A recently published retrospective study conducted in Europe evaluated the correlation between viral load and disease progression in the Caucasian population[44]. The results support the findings of the REVEAL HBV study; concluding that the risk of liver-related mortality in Caucasian adults with CHB is correlated with sustained disease activity and ongoing high level of HBV replication independently of HBeAg status.

In the base-case analysis, treatment-induced viral suppression was assumed to result in a decrease in the risk of cirrhosis. A pooled analysis of clinical trials conducted by Goodman et al. found a reduced risk of cirrhosis (2%) with 1-year of lamivudine treatment[115], and previous cost-effectiveness analyses by Shepherd et al.[55] and Crowley et al.[96] have included this effect in their analyses. In order to calculate the risk reduction for all interventions in this analysis, the viral suppression data from the network meta-analysis was used in combination with the results of the REVEAL study[40]. The table below shows the annual cirrhosis risk estimates from the REVEAL study[40].

Table 6.8: Cirrhosis risk from REVEAL–HBV Study[40].

HBV DNA range (copies/mL)	Relative risk	Cirrhosis risk [a]
0–299	1.0	0.42%
300–9,900	2.0	0.83%
10,000–99,000	3.6	1.49%
100,000–990,000	9.7	4.03%
≥1,000,000	10.6	4.40%

[a] Cirrhosis risk was calculated using the following equation: $y = -0.003x^3 + 0.0357x^2 - 0.1233x + 0.135$, $R^2 = 0.9764$ where y = cirrhosis risk and x = HBV DNA ($\log_{10}$)

The method used to calculate the risk reduction for individuals receiving either entecavir or lamivudine and who did not seroconvert in year 1 was as follows. Patients who did not seroconvert but achieved undetectable HBV DNA (<300/400 copies/mL) were estimated to have a cirrhosis risk of 0.42% during the first year of treatment (50.5% vs. 17% for entecavir vs. lamivudine based on network meta-analysis)[40]. Patients who did not seroconvert and did not achieve undetectable HBV DNA were assigned a cirrhosis risk based on their average viral load, with risk being calculated from the cirrhosis risk equation in Table 6.8 (approximately 1000 copies/mL and 0.8% risk for entecavir, and 22,000 copies/mL and 2.8% risk for lamivudine). The average viral load for entecavir (approximately 1000 copies/mL) and lamivudine (22,000 copies/mL) was estimated from the 022 trial[56].

The risk of cirrhosis was weighted by the proportion of patients not seroconverting during the first year of therapy (50.5% with undetectable and 31.2% with detectable viral load for entecavir and 17% with undetectable and 64.7% with detectable viral load for lamivudine) to give 0.6% and 2.2% for entecavir and lamivudine respectively. The weighted risks of cirrhosis in non-seroconverted patients during the first year of therapy were thus 0.6% and 2.2% for entecavir and lamivudine respectively (Table 6.4 reports the weighted relative risks of cirrhosis, i.e. relative to baseline risk of 4.4%). As a validity check of the REVEAL risk algorithm, the estimate of 2.2% derived using this method for lamivudine corresponded with clinical data of 2% from Goodman et al.[115]. A similar calculation was performed for telbivudine and pegIFN to generate the values used in the model. This used year 1 seroconversion and undetectable viral load data from the network meta-analysis, and average viral load from Lau et al.[19] for pegIFN, and Han et al[72] and Lai et al[73] for telbivudine.

In the base case, it was assumed that all non-seroconverted patients returned to baseline cirrhosis risk of 4.4% after the first year of treatment, even if they continued therapy, although it might be expected that this reduced risk might also apply to the second year of treatment.

HBeAg-positive model: lamivudine-refractory patients

CHB to seroconversion: Entecavir was compared with ADV/LVD combination therapy in HBeAg-positive patients. The probability of seroconversion for entecavir in years 1 and 2 (8% and 8.7%, respectively) was obtained from study 026 as outlined in Table 5.8 in Section 5.4.4. For ADV/LVD combination therapy, Peters et al.[81] and Perrillo et al.[82] both report 1-year seroconversion rates for combination therapy (8% and 6%, respectively). On the basis of these estimates, a mid-point value of 7% was applied during year 1. As there is no information on seroconversion rates for year 2, the assumption was made that the year 1 value of 7% would hold for year 2.

CHB to resistance: Cumulative probability of viral rebound due to genotypic resistance at years 1 and 2 of therapy is 1% and 10% respectively for entecavir (see Table 5.8.5). The annual probability of entecavir resistance was estimated to be 1% and 9.3% for years 1 and 2, respectively. For ADV/LVD combination therapy, Peters et al.[81] and Perrillo et al.[82] do not report on rates of resistance, however, in a retrospective cohort analysis comprising 46% of HBeAg-positive patients (and with a mean duration of 30.4 months), Buti et al. report an overall estimated yearly incidence of 7.4% resistance with adefovir salvage therapy[54]. As such, 7.4% rate was assumed for years 1 and 2 for the ADV/LVD combination.

CHB to cirrhosis (cirrhosis risk reduction): The method used is the same as described above for the NA-naïve, HBeAg-positive patients. For entecavir, viral suppression data from study 026[62] was used in combination with the REVEAL study[40] to obtain estimates of cirrhosis risk for year 1. For the ADV/LVD combination, viral suppression data from Perrillo et al.[82] was used (as this study reported proportion of patients achieving undetectable viral load <200 copies/mL) in combination with the REVEAL study[40] to obtain estimates of cirrhosis risk for year 1.

HBeAg-negative model: treatment-naïve patients

In this model, the key parameters used to assess treatment effect are the proportion of individuals who respond to therapy as defined by achieving undetectable HBV DNA levels (<300/400 copies/mL), treatment durability and drug resistance.

CHB to response: The response rates for years 1 and 2 reported in Table 6.5 were all derived as part of the network meta-analysis. Due to a paucity of data, these rates were assumed to hold for years 3–5.

Patients who do not respond to pegIFN after the designated 48 weeks of therapy go on to receive lamivudine therapy (followed by add-on adefovir salvage if resistance to lamivudine develops) in the second year. As there are no data on the response rates for lamivudine treatment following a switch from pegIFN treatment, response rates were assumed to be the same as for a treatment-naïve patient starting on lamivudine treatment. This is a favourable assumption for pegIFN as sequential therapy (ADV/LVD combination and entecavir switch following lamivudine nonresponse) has not been proven to be superior to monotherapy in inducing a higher rate of sustained response[5].

Patients who become resistant to first-line antiviral therapy and go on to receive add-on salvage therapy (adefovir) are assumed to have a response rate of 60% per year, a value derived from recent trials. A study of 46 HBeAg-negative patients with phenotypic lamivudine resistance by Lampertico et al. found that 62% of patients achieved HBV DNA negativity by 12 months with ADV/LVD salvage therapy, increasing to 78% at 24 months[52]. A study of 49 HBeAg-negative patients by Vassiliadis et al. found that 57% of patients were HBV DNA-negative after 52 weeks of ADV/LVD salvage therapy[116]. Rapti et al. found that 68% of patients were HBV

DNA-negative (<1000 copies/mL) at 1 year and 83% at 2 years with ADV/LVD combination therapy[50]. Thus, a response rate of 60% per year was used, giving a cumulative response of 84% with 2 years of salvage treatment.

Treatment durability (response to CHB): Patients who respond to therapy are assumed to maintain response for as long as they are on treatment. The estimate of treatment durability after cessation of therapy was based on a long-term study by Hadziyannis et al.[80]. In this study, 33 HBeAg-negative patients were treated with adefovir for 4–5 years. It was found that two-thirds of patients maintained normal ALT levels and serum HBV DNA levels $<5\times10^4$ copies/mL for periods of 15–20 months when adefovir treatment was stopped and one-third became HBV DNA negative at follow-up[80]. A 30% durability rate was assumed across all therapies in the year after the 5-year treatment was stopped. Expert clinical opinion was also sought on this data input from clinicians [redacted] who advised that 30% durability would be a reasonable base case and that durability of 10–20% should be explored in the sensitivity analyses.

CHB to resistance: Long-term data show that the cumulative probability of resistance over 4 years of therapy is approximately 1% for entecavir (see Section 5.8.5). An annual resistance rate of 0.2% was estimated for entecavir. For lamivudine, Di Marco et al. report a cumulative incidence of lamivudine resistance of approximately 11% in year 1 and 36% in year 2[106]. As such, the probability of lamivudine resistance was estimated to be 11% in year 1 and 28% in year 2. Resistance values for telbivudine were taken from the GLOBE study, with Lai et al. reporting resistance rate of 2% in year 1[73] and Han et al. reporting cumulative resistance rate of 9% in year 2[72]. The annual probability of telbivudine resistance was estimated to be 2% in year 1 and 7% in year 2.

The rates of resistance in years 3–5 are assumed to be the same as in year 2 for all interventions. Resistance to adefovir salvage therapy was assumed to be 0%.

6.2.8.3 Linking intermediate outcome measures to final outcomes

Were intermediate outcome measured linked to final outcomes (such as patient survival and QALYs)? If so, how was this relationship estimated? What sources of evidence were used, and what other evidence is there to support it?
During each model cycle, the health states used in the models were linked to the final outcome of QALYs by multiplying the proportion of cohorts in that health state by the respective utlity score. The discounted sum of each individual health state then gives the QALYs for each comparator in the model. HBV DNA suppression and HBeAg seroconversion – both key parameters in generating the transition probabilities between health states – were not explicitly linked to final outcomes in either of the models.

6.2.8.4 Inclusion of health effects/adverse effects

Were the health effects or adverse effects associated with the technologies included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost-effectiveness of the technology?
The adverse events associated with antiviral agents (entecavir, lamivudine and telbivudine) are rare, and as such their inclusion would have a negligible impact on the estimated cost-effectiveness of entecavir. Therefore, they were not included in the economic evaluation. This is consistent with other economic evaluations identified in Section 6.1 and is also in line with Shepherd et al.[55].

In contrast, the adverse effects associated with pegIFNα-2a were included in the economic evaluation by incorporating a small utility decrement for the duration of treatment (i.e. 1 year). This approach is in line with previously published cost-effectiveness study of pegIFNα-2a[76]. The inclusion of costs associated with adverse does not impact the estimated cost-effectiveness of entecavir.

6.2.8.5 Was expert opinion used to estimate any clinical parameters?

If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?
Expert opinion was not used to estimate clinical parameters. They were obtained from manufacturers' clinical trials, published studies and publicly available sources (e.g. UK government mortality data, and the BNF[3]).

6.2.8.6 Additional assumptions regarding clinical evidence

What remaining assumptions regarding clinical evidence were made? Why are they considered reasonable?
The key assumptions underlying both models are summarised in Section 6.2.7.4 (Tables 6.6 and 6.7).

6.2.9 Measurement and valuation of health effects

Health effects are assessed using QALYs, as per the NICE reference case[77].

6.2.9.1 Health effects included in the model

Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.
HBV DNA suppression, HBeAg seroconversion and antiviral resistance were measured in clinical trials, as described in the trials listed in Section 5.3.1.

6.2.9.2 Valued health effects

Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?
Utilities corresponding to the following health states were elicited: CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated cirrhosis, non-replicating cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation. Measures of HR-QoL were not elicited within the trials and values used were obtained directly from a utility study described below. Instead of applying fixed decrements to age-specfic baseline utilities, fixed values were applied to each health state.

The utility study by Levy et al. reports utilities for both CHB and a range of liver-related diseases[79]. Values were elicited from a representative sample of 100 uninfected individuals (societal group) in the UK using the standard gamble method. The age- and sex-adjusted results showed that in comparison with CHB, individuals who develop compensated cirrhosis experience a very slight decrease in HR-QoL (CHB 0.88, CC 0.87) whereas those who develop either HCC or DCC experience significant reductions in their quality of life (HCC 0.42, DCC 0.36). A description of

the vignettes used in the elicitation of all utilities can be found in the manuscript[79]. In the assessment by Shepherd et al. decrements were applied to population norms, with CHB being given a slight decrement (–0.04)[55]. The remaining utility decrements were derived from studies in either patients with hepatitis C or liver transplant patients.

Utility values for HBeAg seroconversion, HBsAg loss or response states were not elicited as part of the utility study by Levy et al.[79] and were assumed to be no different to those of a normal individual. This is consistent with utility assumptions made by Shepherd et al.[55] for NICE TA96[4]. UK published tariff on the five-dimensional European Quality of Life scale (EQ-5D) for individuals aged 35–44 years (Kind et al.[117]) were applied to these states.

As mentioned in 6.2.8.4, the reduction in HR-QoL associated with the adverse effects of pegIFNα-2a was included in the base case analysis through a utility decrement applied to the CHB state for the duration of therapy. The value used was taken from a recently published cost-utility analysis[76]. The disutlity with pegIFNα-2a therapy was not included in the analysis by Shepherd et al. where no treatment decrements were applied[55]. The impact of removing this utility decrement was explored during sensitivity analyses.

Table 6.9: Estimated health state utilities used in evaluation.

Health state	Utility	Comments	Source
CHB	0.88		Levy et al.[79]
Seroconversion	0.91	Only applies to the HBeAg-positive model	Kind et al.[117]
Response	0.91	Only applies to the HBeAg-negative model	Kind et al.[117]
HBsAg seroconversion	0.91	Assumed to be the same as HBeAg seroconversion value; applied to both models	Kind et al.[117]
Flare	0.36	Assumed to be the same as DCC	Levy et al.[79]
Resistance	0.88	Assumed to be the same as CHB utility	Levy et al.[79]
CC	0.87		Levy et al.[79]
CCNR	0.88	Assumed to be the same as CHB	Levy et al.[79]
DC	0.36		Levy et al.[79]
HCC	0.42		Levy et al.[79]
LT	0.69		Levy et al.[79]
Post-LT	0.82		Levy et al.[79]
Adverse events from treatment	0.05	Applied only to patients on pegIFN therapy	Veenstra et al.[76]

CC: compensated cirrhosis; CCNR: Nonreplicating compensated cirrhosis; CHB: chronic hepatitis B; DCC: decompensated cirrhosis; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HCC: heptocellular carcinoma; LT: liver transplant; pegIFN: pegylated interferon.

6.2.9.3 Consistency with NICE reference case

Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?
Values were measured and evaluated in line with NICE's reference case[77].

6.2.9.4 Health effects excluded from the model

Were any health effects excluded from the analysis? If so, why were they excluded?
Health effects associated with adverse events were not measured for the NAs as these agents are generally well-tolerated and have a good safety profile.

6.2.9.5 Other methods of expressing health effects

If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?
Not relevant. Health effects were expressed using QALYs.

6.2.10 Resource identification, measurement and valuation

6.2.10.1 List of resources included in the evaluation

Table 6.10 lists the drug treatment costs and health state costs used in the evaluation. Drug treatment costs were taken from the latest version of the BNF[3]. Standard dosage and full compliance were assumed in the derivation of the annual cost. The assumption was made that there was no difference in the physician visits or laboratory monitoring costs between the drugs. Shepherd et al. estimated a total of 16 outpatient visits in a year for a patient on pegIFN therapy as opposed to 11 visits for a patient on antivirals[55]. Their exclusion may underestimate cost-effectiveness of entecavir versus pegIFN but does not impact the overall estimated cost-effectiveness of entecavir.

Where possible, health state costs were taken from the model published by Shepherd et al. in February 2006[55]. These costs were inflated to reflect 2007 prices using a GDP deflator[118] under the assumption that service provision had not changed significantly in the last 2 years. Shepherd et al. state that the original values "were a combination of values estimated specifically for this assessment, based on treatment protocols developed with expert advisors to the project and costed with the assistance of the finance department at Southampton University Hospitals Trust, and published cost estimates for the progressive stages of liver disease"[55].

Table 6.10: Drug acquisition costs used in the evaluation

Resource	Annual unit cost (£)	Source	Comments
Treatment costs			
Entecavir	4,599	BNF[3]	30-tablet pack 0.5 mg qd: £378.00 (same cost for 1 mg qd for lamivudine-refractory patients)
Telbivudine	3,785	BNF[3]	28-tablet pack 600 mg qd: £290.33
Lamivudine	1018	BNF[3]	28-tablet pack 100 mg qd: £78.09
pegIFNα-2a	6,339	BNF[3]	180-mg prefilled syringe: £132.06 (one syringe per week)
Adefovir	3,833	BNF[3]	30-tablet pack 10 mg qd: £315.00
Health state costs			
CHB	565	Shepherd et al.[55]	Inflated to 2007 equivalent
HBeAg Seroconverted	281	Shepherd et al.[55]	Inflated to 2007 equivalent; only applies to the HBeAg-positive model
CHB to response (undetectable	281	Assume same as HBeAg seroconverted	Shepherd et al.[55], inflated to 2007 equivalent

HBV DNA)			
HBsAg seroconverted	32	Shepherd et al.[55]	Inflated to 2007 equivalent Based on an individual requiring one physician visit per year
Flare	9,600	Assumed same as DCC	Shepherd et al.[55], inflated to 2007 equivalent
Resistance	565	Assumed same as CHB	Shepherd et al.[55], inflated to 2007 equivalent
CC	1,198	Shepherd et al.[55]	Inflated to 2007 equivalent
Inactive cirrhosis	565	Assumed same as CHB	Shepherd et al.[55], inflated to 2007 equivalent
DCC	9,600	Shepherd et al.[55]	Inflated to 2007 equivalent
HCC	8,554	Shepherd et al.[55]	Inflated to 2007 equivalent
LT	38,723	Shepherd et al.[55]	Inflated to 2007 equivalent
Post-LT	1,457	Shepherd et al.[55]	Inflated to 2007 equivalent

CHB: chronic hepatitis B; DCC: decompensated cirrhosis; CC: compensated cirrhosis; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; LT: liver transplant; qd: once daily.

6.2.10.2 How were the resources measured?

Drug costs were estimated according to recommended dose from their respective SmPCs[1 17 18 23 24] and obtained from the most recent version of the BNF[3]. Where possible, health state costs were taken from Shepherd et al.[55] and inflated to 2007 equivalents assuming service provision remained unchanged in the intervening period. The remaining values were derived from previously published analyses.

6.2.10.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No. The treatment specific risk of disease progression was measured in clinical trials and baseline risks were derived from a systematic review of the literature and previous CHB cost-effectiveness analyses (see Tables 6.3–6.5). Resource use was not measured in entecavir trials and was not derived from the same sources as baseline risks. Health state costs were taken from Shepherd et al.[55] (see Table 6.10).

6.2.10.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes. In the HBeAg-positive model, 2-year treatment duration was assumed and treatment costs were applied during each cycle where treatment was provided. The additional costs of salvage therapy were allocated separately for the duration of salvage treatment only to those that received both therapies. Costs associated with individual health states were applied for the whole duration of the model.

In the HBeAg-negative model, the treatment duration of both first-line and salvage therapies were restricted to a maximum defined duration of 5 years. Treatment and health state costs were applied as required per cycle, with the additional cost of salvage therapy being incurred by those requiring the additional therapy.

6.2.10.5 What source(s) of information were used to value the resources?

See Table 6.10 in Section 6.2.10.1.

6.2.10.6 Unit cost (excluding VAT) of the intervention(s)

What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?
See Table 6.10 in Section 6.2.10.1.

6.2.10.7 Consistency with the NICE reference case

Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?
Yes.

6.2.10.8 Were resource values indexed to the current price year?

Drug acquisition costs were taken from the most recent version of the BNF, which reflects the most up-to-date information[3]. Health state costs were inflated to their 2007 price year equivalents using a GDP deflator under the assumption that service provision had not changed significantly in the last 2 years[118].

6.2.10.9 Assumptions made in estimating resource management and valuation.

Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.
The following assumptions were made about resource use:

i) All patients take the recommended daily dose for the whole of the year.
ii) The costs used in the previous STA submission[55] reflected current UK practice as of 2005 and it was assumed here that clinical practice has not changed significantly in the intervening 2 years.
iii) For each pairwise comparison undertaken, the incremental costs associated with monitoring and side effects are assumed to be zero, i.e. the same for each intervention under consideration.
iv) Breaks in treatment do not occur.
v) Future costs are assumed to be the same as current prices, and no new entrants are assumed to enter the market. Drugs are also not assumed to go off licence. Given that medical costs can be expected to increase with time, this is a simplification of reality. The effect of this assumption is unknown.

6.2.11 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?
Costs and benefits were discounted at 3.5% in both models as per the reference case[77]. Other rates were tested in sensitivity analyses.

6.2.12 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.12.1 Variables subjected to sensitivity analysis

Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?
All variables were subject to one-way sensitivity analysis and varied over the ranges as described in 6.2.7.3. This identified the key variables that over their uncertainty range had the greatest impact in the variability on the incremental cost/QALY results. The key variables and the main findings from the sensitivity analysis are explained in Section 6.3.3.1.

6.2.12.2 Probabilistic sensitivity analysis

Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.
Probabilisitic sensitivity analysis was undertaken. With the exception of results derived from the network meta-analysis, beta distributions are assigned to all transition probabilities and log-normal distributions to all relative risks. For results derived from the network meta-analysis, normal distributions are used to sample values for both log-odds and log-odds ratios, and these values are then used to generate the relevant transition probabilities.

The full list of costs used in both models is given in Section 6.2.10.1. Drug costs are assumed to be known with certainty and thus have no associated distributions. Uncertainty surrounding health state costs are represented using log-normal distributions, with a range of ±25% of the central estimate being used to generate 95% CIs.

The full list of utilities used in the models is reported in Section 6.2.9.2. Unless otherwise stated, uncertainty is represented using beta distributions, with a range of ±5% being used to generate 95% CIs for health state utility decrements.

6.2.12.3 Structural uncertainty

Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?
Economic modelling of treatments for CHB is complex, due to both the nature of the disease and a wide range of available treatment patterns. Separate models for HBeAg-positive and -negative disease were developed. The HBeAg-negative form of the disease usually represents a later stage in the course of CHB infection, as patients tend to be both older and have more advanced liver disease than those who are HBeAg positive. Therefore, some of the transition probabilities between health states for both patient groups can be expected to differ. Furthermore, both treatment continuation and duration may differ in both patient groups, with HBeAg-negative patients requiring long-term therapy so as to achieve sustained virological remission.

Structural uncertainty with respect to modelling approach was not explored in this submission. As discussed in Section 6.2.7, most widely used approaches have been Markov models (previously applied for a HTA undertaken by NICE to assess technologies for the treatment of CHB[55]). The Markov framework allows a realistic representation of the disease and avoids over-simplifications while remaining transparent. Furthermore, it is unlikely that the overall cost-effectiveness would be radically different because the results of this evaluation are broadly in line with those of NICE technology appraisal 96[4].

The base case of this analysis estimates cost-effectiveness of entecavir over the patient's lifetime to reflect the reference case[77]. For the positive model, 2-year

treatment duration was used (in-line with entecavir's key Phase 3 trial duration[56]) and the benefits associated with drug therapy were limited to 2 years only. HBeAg-negative disease patients require long-term therapy and 5-year treatment duration (with benefits limited to 5 years) was used as the base case in this submission. However, efficacy data used in the model was taken from 2-year trials[61 63]. Extrapolating clinical effectiveness over very long timeframes relies on assumptions that cannot be validated. The effect of increasing duration of treatment from 5 years to lifetime in the HBeAg-negative patients was investigated as a scenario analysis and showed that increasing treatment duration to lifetime increased the ICER for entecavir but at levels below £20,000 per QALY.

This submission reflects the NICE reference case[77], with perspective restricted to the NHS and PSS. Indirect costs resulting from CHB infection, such as productivity loss and loss of income, have not been factored into the base case and this likely underestimates the costs of the disease, benefits and therefore the cost-effectiveness of entecavir.

6.2.13 Statistical analysis

6.2.13.1 Transition probabilities

How were rates or probabilities based on intervals transformed into (transition) probabilities?
The 1-year cycle length of the model was chosen to correspond with the interval results reported in clinical trial results so probabilities could be directly used in the model. When it was necessary to convert rates and/or probabilities from interim timepoints, the following formulae were used:

$r = – [\ln (1 – P)] / t$

To convert a rate back to probability assuming an event occurs at a constant rate (r) over a time period (t) the following was used:

$p = 1 – \exp \{-rt\}$

where r = rate and p = probability

6.2.13.2 Changes in transition probabilities over time

Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.
Where there was evidence that treatment-related transition probabilities varied over time, this was included in the evaluation. There is a lack of evidence on the variability over time of the disease transition probabilities and therefore these were kept constant.

6.2.14 Validity

The following steps have been taken during and after the development of the model to validate and check the analysis:

- Expert clinical opinion leaders [redacted]

[redacted]: internal BMS staff) were consulted before and during the development process to validate the structure and key assumptions of the model to ensure clinical validity.

- Inputs in the model were compared with previous CHB model developed by SHTAC for NICE technology appraisal 96 to ensure consistency[4 55]. The results were also compared with previous models to check they were of a similar order.
- Systematic review of published economic evaluations of CHB treatment was conducted and results were used to validate assumptions in the model, e.g. risk of cirrhosis, spontaneous HBeAg seroconverison, treatment durability after long-term antiviral therapy, and others.
- The model has been reviewed by an independent statistician and a modeller not involved in the development or analyses.
- The results of the model are consistent with those of other published economic evaluations of treatments for CHB (see Section 6.1.2)

6.3 Results

6.3.1 Base-case analysis

The results for the base case analyses are presented below.

Table 6.11 shows that compared with lamivudine, entecavir is a cost-effective first-line therapy for HBeAg-positive patients with an incremental cost per QALY of £14,329. Similarly, for the comparison with PegIFN, the cost per QALY for entecavir is £8,403, which is much lower than the £20,000 per QALY threshold. Entecavir is comparable to telbivudine in QALYs and costs, with the overall ICER sensitive to these small differences.

Table 6.11: Cost-effectiveness results for entecavir as first-line antiviral therapy in HBeAg-positive disease.

	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	16.84	8,212	14,833	23,045	–
Lamivudine	16.61	4,164	15,620	19,784	14,329
pegIFN	16.64	6,339	15,057	21,396	8,403
Telbivudine	16.84	8,028	14,830	22,858	Telbivudine dominant

HBeAg: hepatitis B e antigen; ICER: incremental cost-effectiveness ratio; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

Table 6.12 shows that entecavir is also a cost-effective first-line antiviral therapy in HBeAg-negative disease patients when duration of treatment is assumed to be 5 years only. The incremental cost per QALYs are all below £20,000.

Table 6.12: Cost-effectiveness results for entecavir as first-line antiviral therapy in HBeAg-negative disease (5-year treatment duration).

	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	14.41	19,562	18,887	38,449	–
Lamivudine	13.80	9,107	21,163	30,270	13,208
pegIFN	13.71	11,779	21,363	33,142	7,511
Telbividine	14.21	17,354	19,674	37,028	6,907

HBeAg: hepatitis B e antigen; ICER: incremental cost-effectiveness ratio; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

Table 6.13 shows that in a lamivudine-resistant or refractory population, entecavir is cheaper and more effective than ADV/LVD combination therapy. Entecavir provides more QALYs and is approximately £1,000 cheaper per patient over the time horizon chosen, and therefore, is dominant over ADV/LVD combination therapy.

Table 6.13: Cost-effectiveness results for entecavir as antiviral therapy for lamivudine-refractory patients.

	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	16.43	8,932	16,182	25,114	–
Adefovir + lamivudine	16.36	9,621	16,494	26,116	Entecavir dominant

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

6.3.2 Subgroup analysis

As stated in Section 6.2.3, no subgroup analyses were conducted.

6.3.3 Sensitivity analyses

6.3.3.1 One-way sensitivity analyses

One-way sensitivity analyses were performed on all parameters from this economic analysis, as explained in Section 6.2.12.1. The results for the key parameters (varied within the range of uncertainity) that had the greatest impact on the incremental cost/QALY results are presented in Tables 6.14 and 6.15 for HBeAg-positive and HBeAg-negative patients, respectively.

Results are presented for entecavir versus lamivudine comparision only. The positive model was most sensitive to baseline disease transition probabilities for CHB to seroconversion, HCC and risk of cirrhosis, followed by estimates of treatment effectiveness. The model was also sensitive to the discount rate for benefits and utilities. However, most of the incremental cost per QALYs are below £20,000.

The sensitivity analyses for entecavir versus pegIFN typically show a similar pattern to those presented below for HBeAg-positive patients for entecavir versus lamivudine. Sensitivity analyses of entecavir versus telbivudine showed the results were highly sensitive to variation in a large number of parameters with the resultant ICERs varying between entecavir and telbivudine being dominant. Overall, entecavir and telbivudine are clinically equivalent with small differences in costs, which suggests that their cost-effectiveness is comparable. The results of the one-way sensitivity analyses versus pegIFN and telbivudine are presented in Appendix 8.8.

Table 6.14: Results of one-way sensitivity analyses for entecavir versus lamivudine as first-line antiviral therapy in HBeAg-positive patients.

Base case ICER £14,329/QALY		Low value			High value		
Parameters	**Base value**	**Value**	**ICER (£/QALY)**	**% change**	**Value**	**ICER (£/QALY)**	**% change**
Baseline cirrhosis risk	0.044	0.004	48,797	241	0.084	9,541	-33
CHB to SC, baseline	0.090	0.060	29,388	105	0.120	9,647	-33
Inactive cirrhosis to DC, baseline	0.050	0.000	20,590	44	0.075	13,013	-9
CHB to SC, lamivudine year 1	0.183	0.130	8,831	-38	0.240	28,984	102
CHB to SC, entecavir year 1	0.183	0.150	21,868	53	0.220	9,591	–33
CHB to SC, lamivudine year 2	0.072	0.010	10,878	-24	0.160	23,456	64
CHB to SC, entecavir year 2	0.104	0.060	21,220	48	0.160	9,629	-33

Resistance utility	0.880	0.836	10,250	–28	0.924	23,798	66
CHB utility	0.880	0.836	22,859	60	0.924	10,435	–27
Discount rate, benefits	0.035	0.000	5,657	–61	0.060	24,422	70
Discount rate, costs	0.035	0.000	12,163	-15	0.060	15,123	6

CC: compensated cirrhosis; CHB: chronic hepatitis B; HBeAg: hepatitis B e angitgen; HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SC: seroconversion.

Table 6.15 shows the results for the entecavir and lamivudine comparison. The negative model was most sensitive to estimates of treatment relapse but relatively robust for all other parameters when varied within acceptable ranges.

Table 6.15: One-way sensitivity analyses for entecavir versus lamivudine as first-line antiviral therapy in HBeAg-negative patients

Base case ICER£13,208/QALY		**Low value**			**High value**		
Parameters	**Base value**	**Value**	**ICER (£/QALY)**	**% change**	**Value**	**ICER (£/QALY)**	**% change**
Treatment relapse, baseline	0.7	0.500	9,944	-31	0.900	18,335	28
CC to DCC	0.05	0.000	24,485	71	0.075	11,674	-19
Response to HCC	0.003	0.000	11,789	-18	0.009	17,115	19
CC to HCC, baseline	0.022	0.005	18,167	–3	0.039	12,758	–32
CHB treatment to CC, lamivudine year 1	0.090	0.057	18,550	29	0.123	10,392	-27
CHBtx to CC, entecavir year 1	0.090	0.057	10,546	-26	0.123	17,130	20
Discount rate, benefits	0.035	0.000	6,471	-55	0.060	20,258	41

CC: compensated cirrhosis; CHB: chronic hepatitis B; DCC: decompensated cirrhosis; HBeAg: hepatitis B e antigen; HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

6.3.3.2 Probabilistic sensitivity analyses (PSA)

HBeAg-positive, treatment-naïve patients

The probabilistic analysis results demonstrate that entecavir is a cost-effective treatment option with a probability of the incremental cost per QALY being below a £20,000 threshold of 57% versus lamivudine and 82% versus pegIFN (Table 6.16). In terms of cost-effectiveness of entecavir versus telbivudine, the probabilistic sensitivity analysis demonstrates that entecavir and telbivudine are comparable in this patient population with a 19% probability that entecavir is dominant and 45% probability that entecavir falls under £20,000/QALY as shown in Table 6.16. This is also demonstrated in the scatterplot in Figure 6.4. As such, in terms of cost-effectiveness in the HBeAg-positive population, telbivudine and entecavir are comparable.

Cost-effectiveness acceptability curves in Figure 6.5 demonstrate that entecavir has a high probability of being cost-effective versus lamivudine and PegIFN at the £30,000/QALY willingness-to-pay threshold. In the comparison with telbivudine, entecavir has an approximately equal chance of being cost-effective at the £30,000/QALY willingness-to-pay threshold.

PSA results vs pegIFN and telbivudine are presented in Appendix 8.8

Table 6.16: Probabilistic analysis results – probabilities of being below cost effectiveness thresholds in the HbeAg-positive population

	Percentage in each category		
	Lamivudine	**pegIFN**	**Telbivudine**
Entecavir dominant	0.0%	0.2%	19.3%
Below £20,000	57.4%	82.0%	45.0%
Below £30,000	76.4%	86.9%	46.5%
Comparator dominant	2.5%	5.6%	48.6%

Table 6.17: Probabilistic analysis results – total costs and QALYs for all comparators in HBeAg positive population.

	Total cost (£)		QALYs	
	Mean	**95% CI**	**Mean**	**95% CI**
Entecavir	22,705	(19,212, 26,906)	16.96	(15.42, 18.28)
Lamivudine	19,506	(16,672, 22,834)	16.75	(15.44, 17.88)
pegIFN	21,343	(18,929, 24,136)	16.75	(15.51, 17.83)
Telbivudine	22,070	(18,109, 25,702)	16.97	(15.65, 18.15)

CI: confidence interval; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

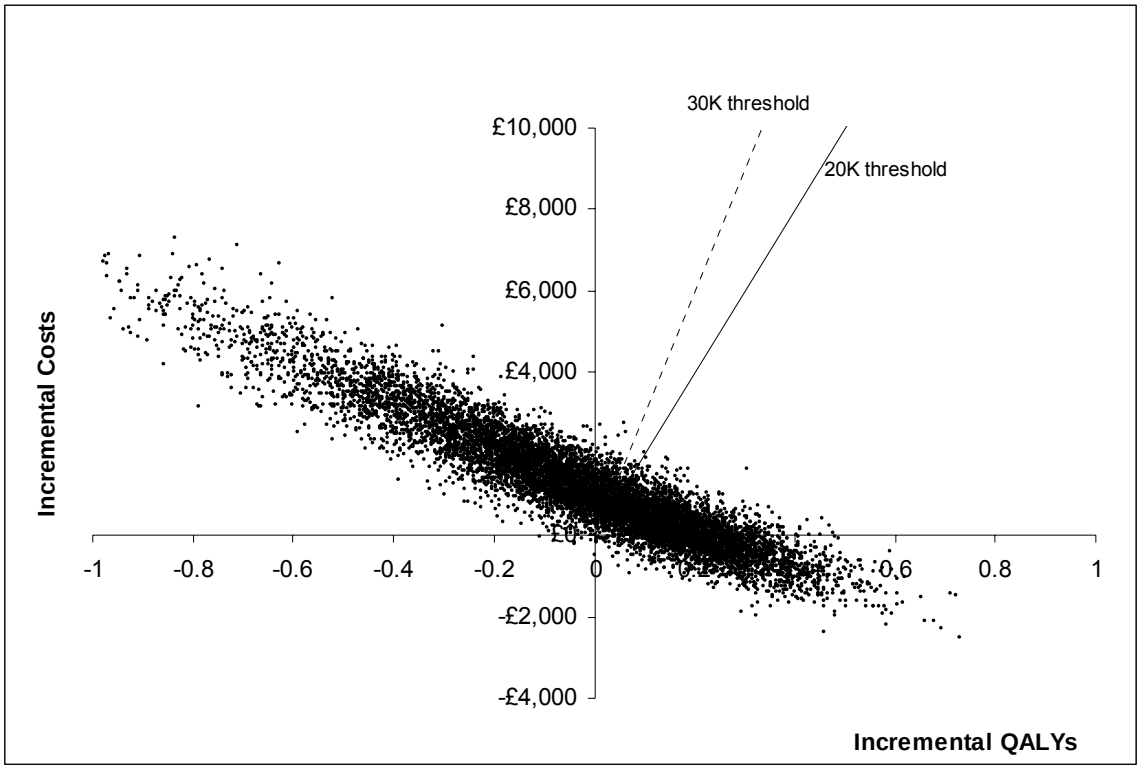


Figure 6.4: Scatter plot for entecavir vs. telbivudine (10,000 simulations)

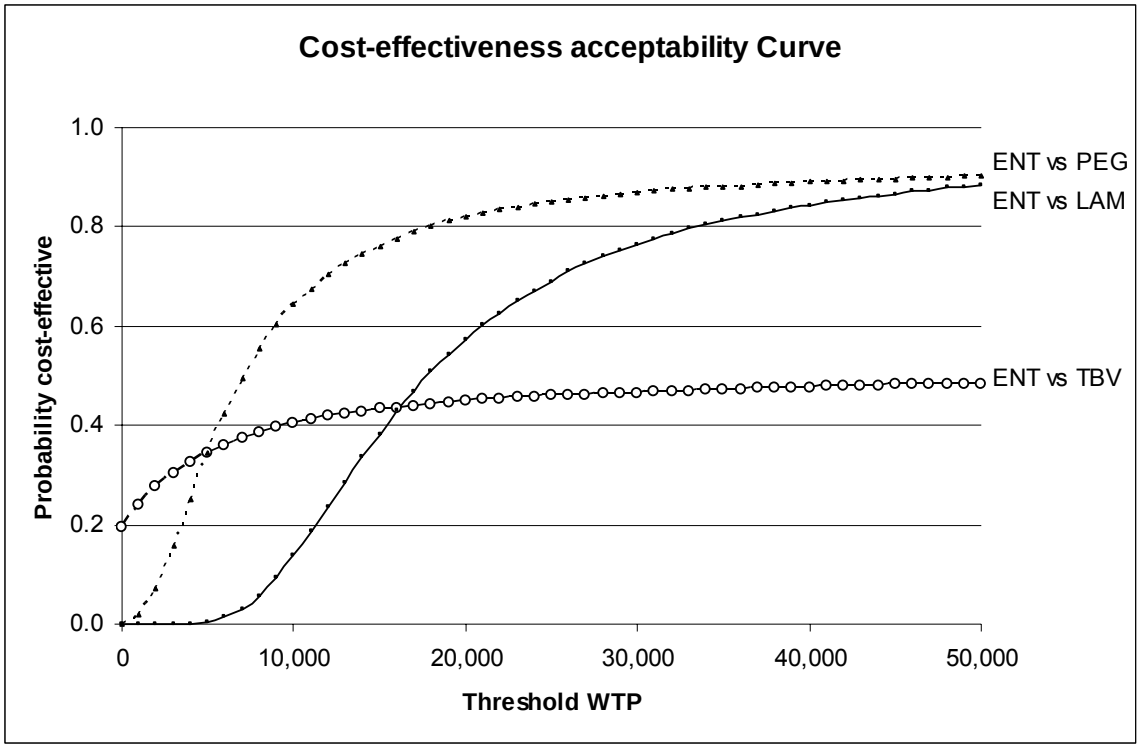


Figure 6.5: Cost-effectiveness acceptability curves – HbeAg-positive population.

ENT: entecavir; LAM: lamivudine; PEG: pegylated interferon; TBV: telbivudine; WTP: willingness-to-pay.

HBeAg-negative, treatment-naïve patients

The probabilistic analysis results demonstrate that entecavir is a cost-effective treatment option for this patient group with a high probability of falling below a £20,000 threshold of 90% compared with lamivudine, 100% compared with pegIFN and 96% compared with telbivudine (Table 6.18). Cost-effectiveness acceptability curves in Figure 6.6 demonstrate that entecavir has a high probability of being cost-effective versus all three comparators: lamivudine, PegIFN and telbivudine at the £30,000/QALY willingness-to-pay threshold.

Table 6.18: Probabilistic analysis results – probabilities of being below cost effectiveness thresholds in the HbeAg-negative population.

	Percentage in each category		
	Lamivudine	**PegIFN**	**Telbivudine**
Entecavir dominant	0.00%	0.00%	0.5%
Below £20,000	90.4%	99.9%	95.8%
Below £30,000	99.4%	100.0%	99.2%
Comparator dominant	0.0%	0.0%	0.0%

pegIFN: pegylated interferon.

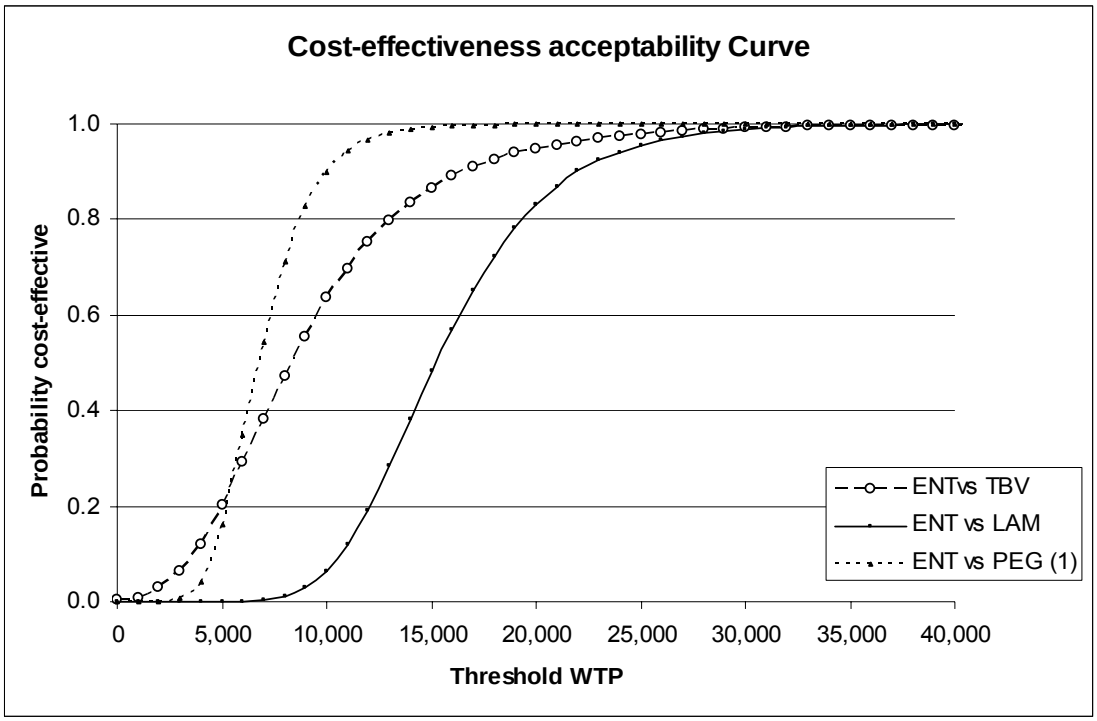


Figure 6.6: Cost-effectiveness acceptability curves – HbeAg-negative population.

ENT: entecavir; LAM: lamivudine; PEG: pegylated interferon; TBV: telbivudine; WTP: willingness-to-pay.

6.3.3.3 Scenario analyses

Additional scenario analyses were conducted to further explore some of the model assumptions and the results of these are shown below.

For the HBeAg-positive model, the scenario in which entecavir is compared with the ADV/LVD combination in a treatment-naïve patient populatin was explored. This resulted in entecavir being a dominant strategy as shown in Table 6.19. An analysis was also conducted assuming no disutility for patients receiving pegIFN treatment. The ICER in this scenario increased from £8,403 to £11,899. This is shown in Table 6.20.

Table 6.19: Cost-effectiveness results for entecavir vs. ADV/LVD combination as first-line antiviral therapy in HBeAg-positive disease

	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	16.84	8,212	14,833	23,045	
ADV/LVD	16.59	8,776	15,544	24,320	Entecavir dominant

HBeAg: hepatitis B e antigen; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

Table 6.20: Cost-effectiveness results for entecavir vs. pegIFN (without utility decrement) as first-line antiviral therapy in HBeAg-positive disease

	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	16.84	8,212	14,833	23,045	
pegIFN	16.70	6,339	15,057	21,396	11,899

HBeAg: hepatitis B e antigen; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

Thirdly, a scenario where patients were assumed to have received 6 months consolidation therapy after HBeAg seroconversion was, with a corresponding 30% relative improvement in treatment durability (i.e. HBeAg seroconversion to CHB state) was analysed. In this scenario, entecavir remained cost-effective, compared with lamivudine and pegIFN, with ICERs higher than the base-case scenario of no consolidation therapy. As in the base case scenario, entecavir and telbivudine are clinically equivalent with small differences in costs (£269 per patient) over the lifetime horizon. Results are presented in Table 6.21.

Table 6.21: Cost-effectiveness results for entecavir with 6 months consolidation therapy

	QALYs	Drug Costs	Health Care Costs	Total Costs	ICER vs Entecavir (cost/QALY)
Entecavir	16.86	£8,798	£14,768	£23,566	
Lamivudine	16.64	£4,273	£15,522	£19,795	£17,284
Peginterferon	16.64	£6,339	£15,057	£21,396	£10,086
Telbivudine	16.86	£8,545	£14,752	£23,297	LdT dominant

HBeAg: hepatitis B e antigen; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

For the HBeAg-negative model, lifetime treatment duration was explored in a scenario analysis as shown in Table 6.22. In this scenario, entecavir remained cost-effective, compared with lamivudine and pegIFN, with ICERs higher than the base-case scenario of 5 years of treatment. Entecavir also became dominant over telbivudine.

Table 6.22: Cost-effectiveness results for entecavir as first-line antiviral therapy in HBeAg-negative disease (lifetime treatment duration)

	Life years	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	18.34	16.42	72,923	9,351	82,274	
Lamivudine	17.63	15.58	55,574	12,586	68,160	16,850
pegIFN	17.38	14.23	55,255	13,749	69,003	11,100
Telbivudine	17.99	16.00	81,503	11,186	92,689	Entecavir dominant

HBeAg: hepatitis B e antigen; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

For comparison, the previous NICE reference case discount rates of 6% for costs and 1.5% for QALYs, used in Shepherd et al.[55], were applied in a sensitivity analysis. The results are shown in Table 6.23.

Table 6.23: Discount rate costs (6%), QALY = 1.5%

	HBeAg-positive	HBeAg-negative (5-year treatment)
Lamivudine	£9,141	£9,454
pegIFN	£6,292	£5,871
Telbivudine	Telbivudine dominant	£5,204

HBeAg: hepatitis B e antigen; pegIFN: pegylated interferon; QALY: quality-adjusted life-year.

6.3.4 Interpretation of economic evidence

6.3.4.1 Consistency with the published economic literature

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from the economic evaluation are consistent with those previously published. Comparison with Shepherd et al.[55] shows that the discounted QALYs estimated are of a similar order, albeit slightly lower for HBeAg-positive patients and slightly higher in HBeAg-negative patients. The total costs that are estimated in the base case are higher than those reported by Shepherd et al.[55] because salvage therapy has been included. Shepherd at al. presented a combined cohort analysis (HBeAg-positive and -negative patients) that included sequential treatment[55]. This combined analysis is not directly comparable with the separate analyses for each patient population but does show increased costs consistent with a weighted average of the results presented in this submission. Furthermore, the analysis in this submission includes more up-to-date data and results from a comprehensive network meta-analysis, so some differences are expected. Although there is some degree of uncertainty in transition probabilities for disease progression, entecavir has been demonstrated to be a cost-effective treatment for CHB and these results are robust to changes in the underlying model assumptions.

HBeAg-positive model

Entecavir is a cost-effective treatment option compared with both lamivudine and pegIFN. Entecavir has higher total costs but improved outcomes relative to lamivudine with an ICER of £14,329. Sensitivity analyses show that this estimate is relatively robust and below the £30,000 threshold, even assuming some extreme values for baseline disease probabilities for CHB to seroconversion, HCC and risk of cirrhosis. Compared with lamivudine, there is a 57% probability that entecavir is cost-effective at the £20,000 threshold. In the comparision with pegIFN, entecavir has higher total costs but improved outcomes relative to pegIFN with an ICER of £8,403.

Probabilistic sensitivity analysis shows an 82% probability that entecavir is cost-effective at the £20,000 threshold.

In the deterministic analysis, entecavir and telbivudine have comparable efficacy with small differences in costs (£187 per patient) over the lifetime horizon. Indeed, sensitivity analysis demonstrates that there is no difference in cost-effectiveness between entecavir and telbivudine and that small changes in a number of parameters will switch the ICER so that entecavir is dominant. This is further evidenced in the probabilistic sensitivity analysis results with the cost-effectiveness acceptability curve levelling at around 50% and the scatterplot distributed around the origin. The network meta-analysis results reported in Section 5.6 demonstrate that entecavir and telbivudine are equivalent with regard to the HBeAg seroconversion endpoint, with entecavir being statistically significantly better than telbivudine in achieving undetectable HBV DNA. Unadjusted indirect comparisons of trial data show that entecavir may be associated with lower rates of resistance compared with telbivudine.

HBeAg-negative model

Entecavir is a cost-effective treatment option compared with lamivudine, pegIFN and telbivudine. Entecavir has higher total costs but improved outcomes relative to lamivudine, pegIFN and telbivudine with ICERs of £13,208, £7,511 and £6,907, respectively. Deterministic and probabilistic sensitivity analyses show that these results are robust with the exception of varying treatment relapse rates, as was also the case in the results reported by Shepherd et al.[55].

In a scenario analysis of lifetime treatment, entecavir remained cost-effective with the ICERs increasing slightly compared with lamivudine and pegIFN, and entecavir became a dominant option versus telbivudine.

6.3.4.2 Relevance to other patient groups

Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

This evaluation is relevant to all other groups of patient eligible for treatment with entecavir. Due to lack of available data, it was not possible to consider the use of entecacvir in HBeAg-negative lamivudine-refractory patients.

6.3.4.3 Critical appraisal of the economic evaluation

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths:

- Lamivudine, the key comparator used in this evaluation, reflects real UK clinical practice and the cost-effectiveness of entecavir compared with lamivudine was based on recent comparative trials of entecavir and lamivudine.
- Additonal analyses were performed to compare cost-effectiveness of entecavir with pegIFN, which is recommended by NICE as an initial option for CHB therapy[4], and telbivudine, which is undergoing a parallel STA.
- Effectiveness of entecavir and comparators has been derived from a network meta-analysis rather than taken from single studies, as has been the case in previously published studies.
- Assumptions used in the model were informed by evidence obtained from a systematic review of published economic evaluations of CHB treatments. When a range of values was available, its impact was tested in sensitivity analysis.

- A wide range of possible uncertainties have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be stable to wide variations in model parameters.
- In a systematic review of the literature in 2005, the NICE technology appraisal group was unable to identify any methodologically robust utility estimates in the area of liver disease. Data relating to chronic hepatitis C and liver transplant outcomes have been used by NICE. A utility study was undertaken to gain specific utility data for CHB to inform this submission.

Weaknesses:

- Resource utilisation could be explored in more detail.
- Analysis of entecavir versus the ADV/LVD combination in lamivudine-resistant patients (HBeAg-positive disease group) should be considered with caution as the use of ADV/LVD combination therapy in this harder-to-treat HBeAg-positive population is limited to very small trials only[69 69].
- There is considerable uncertainty in parameter estimates for disease progression and the incremental cost/QALY results are highly sensitive to these parameters.

6.3.4.4 Further analyses

What further analyses could be undertaken to enhance the robustness or completeness of the results?

Consideration could be given as to whether there is adequate data to conduct a meta-analysis of disease progression probabilities, which may reduce the uncertainty in these parameters.

7 Assessment of factors relevant to the NHS and other parties

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

Entecavir obtained a UK marketing authorisation on 26th June 2006 and is currently available for use in the UK for the treatment of CHB in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. Patients may be treatment naïve or have failed prior HBV therapy. Another CHB agent, telbivudine, received its marketing authorisation in April 2007, and is going through a parallel STA so its place in the management of CHB remains to be determined. Accurate budget impact assessment will only be possible after NICE guidance for both products is published.

The budget impact is analysed for one year following positive NICE guidance and the calculation is adapted from the NICE costing template for TA96[4]. The budget impact analysis looks at the annual net budget impact for entecavir pre- and post-NICE guidance for entecavir and telbivudine. The share of entecavir in the market is assumed to be 0% pre-NICE guidance (this is in line with IMS CHB database analysis[31] that shows that entecavir's share of the market by volume is less than 2%). Assuming entecavir receives positive NICE guidance as a first-line option for anti-viral therapy, it is assumed it will capture the following market share:

- 50% of new patients treated with lamivudine (including patients who have previously failed interferon therapy)
- 2% of patients who started treatment with lamivudine therapy prior to the current year
- 2% of patients treated with ADV/LVD combination salvage therapy

As such, entecavir is expected to be used in 372 patients (or 8.08% of patients treated for CHB) following positive NICE guidance. For the use of entecavir in place of ADV/LVD combination, costs are offset by current estimated expenditure on patients who would otherwise have received ADV/LVD combination.

Two scenarios are analysed. In scenario 1, all patients eligible for entecavir will receive entecavir. In scenario 2, patients eligible for entecavir can receive either entecavir or telbivudine with equal likelihood. In each scenario, the upper and lower bound estimates of net budget impact are explored. The upper bound assumes that entecavir will replace 75% (instead of 50%) market share of new patients who would otherwise have received lamivudine. The lower bound assumes that entecavir will replace 25% (instead of 50%) market share of new patients who would otherwise have received lamivudine.

Net budget impact results are presented in Table 7.1.1. Budget impact was analysed in two ways: using drug costs only and using drug plus monitoring costs. There were no differences in the two analyses as monitoring costs are the same for all therapies except pegylated interferon where a few additional outpatient visits are required. As such, the analysis presented in Table 7.1 reports net budget impact using drug plus monitoring costs.

Table 7.1.1 provides a summary of the estimated budget impact with consideration of the offset of current expenditure on patients who would have continued to receive

lamivudine/adefovir combination therapy. The potential net annual cost is estimated to be £1.3m for entecavir, or £1.1m for entecavir and telbivudine.

Table 7.1.1: Summary of budget impact of introduction of entecavir/telbivudine

Scenario	Estimated budget impact with positive NICE guidance	
	Potential net annual cost without drug costs offsets	**Drug offset**
Entecavir only (1)	**£1.3 million**	Drug costs offsets - £4,032
Lower bound	£0.7 million	
Upper bound	£1.8 million	
Entecavir/Telbivudine with 50% uptakle each (2)	**£1.1 million**	Drug costs offsets - £2,016
Lower bound	£0.6 million	
Upper bound	£1.6 million	

Table 7.1.2 details the number of patients and corresponding costs pre and post positive NICE guidance for entecavir/telbivudine to arrive at the budget impact summarised in table 7.1.1.

Table 7.1.2: Summary of budget impact of introduction of entecavir/telbivudine

4,610 CHB treated patients	Pre-NICE		Post-NICE[1]		Difference	
	No. of Patients	Cost (million)	No. of Patients	Cost (million)	No. of Patients	Cost (million)
Lamivudine - new Patients	620	£1.35	310	£0.67	310	-£0.68
Lamivudine - patients from previous year	2,330	£5.06	2,284	£4.96	46	-£0.1
Adefovir/Lamivudine	803	£4.82	787	£4.73	16	-£0.09
Entecavir (Scenario 1)	0	0	372	£2.14	372	£2.14
Entecavir (Scenario 2)	0	0	186	£1.07	186	£1.07
Telbivudine (Scenario 2)	0	0	186	£0.92	186	£0.92

(1) Potential net annual cost for entecavir only scenario £1.3
(2) Potential net annual cost for entecavir and telbivudine scenario with 50% uptake each £1.1

[1] All post-NICE scenarios assume positive recommendation of entecavir as first-line antiviral therapy

7.2 What number of patients was assumed to be eligible? How was this figure derived?

It is estimated that 372 patients are eligible for entecavir treatment. Figure 7.2 below provides a flow diagram of patients who are likely to receive entecavir post-NICE guidance and Table 7.2 provides detailed calculation with respect to the population of England and Wales and the proportion of patients who are estimated to receive CHB therapy.

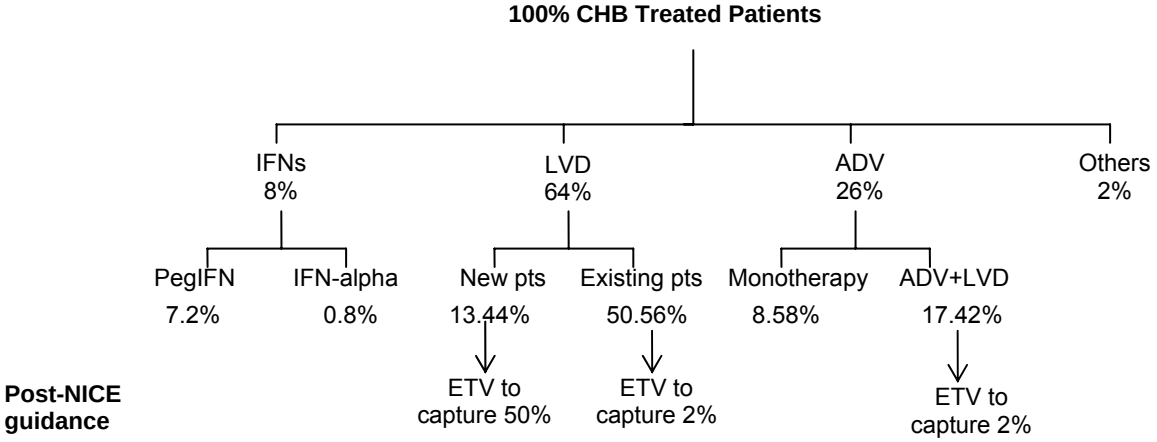


Figure 7.2: Flow diagram of patients who are assumed to receive entecavir (ETV) post-NICE guidance

Table 7.2: Estimated number of patients eligible for entecavir

	Pre-NICE Guidance (No. of patients)	Post-NICE Guidance (No. of patients)	Source/Comments
Total population England and Wales	53,728,800		National statistics[103]
Estimated prevalence of CHB	0.30%		NICE TA96[4]
Total cases of CHB	161,186		Calculated
Adults that are diagnosed with CHB	26%		NICE TA96[4]
% of patients treated for CHB	11%		NICE TA96[4]
Total cases receiving CHB therapy	4,610		Calculated
% patients who receive interferons	8% (369)	8% (369)	Market research**30**
% new patients treated with lamiduvine	13.44% (620)	6.72% (310)	Market research[30]
% patients treated with lamiduvine from previous year	50.56% (2,330)	49.55% (2,284)	Market research[30]
% patients who receive adefovir plus lamiduvine	17.42% (803)	17.07% (787)	Market research[30]
% patients who receive adefovir monotherapy	8.58% (396)	8.58% (396)	Market research[30]
% patients who receive entecavir	**0% (0)**	**8.08% (372)**	**Calculated**
% patients who receive other therapies	2% (92)	2% (92)	Calculated

The recently published Report 'Rising Curve:CHB Infection in the UK' (published by the Hepatitis B foundation in November 2007[119]) estimated the prevalence of CHB in the UK to be approximately 325,000. This equates to a prevalence of approximately 0.6% of the UK population, double the estimate stated in Table 7.2. An alternative scenario assuming 0.6% prevalence is analysed and reported in Appendix 8.9.

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

In addition to assuming that entecavir will receive positive NICE guidance as per the expected indication, the following assumptions have been made in this analysis:

- This budget impact assumes full implementation of NICE guidance.
- Uptake was not phased on the assumption that NICE guidance would be implemented quickly due to unmet need.
- Dose was based on the standard doses described in the relevant SmPC.
- Dose escalation or increased dosing frequency is not explored.
- Analysis does not take into account unlicensed agents and it is assumed that no new therapies become available.

7.4 What assumption(s) were made about market share (where relevant)?

The current market share of CHB therapies, based on market research[30], was assumed to be 8% for interferons, 64% for lamivudine of which 21% are new patients starting on antiviral therapy for the first time, 26% for adefovir of which 67% are on ADV/LVD combination[30] [31]. As mentioned in Section 7.1, an equal split between entecavir and telbivudine is assumed when both agents are considered. This is an assumption and will depend on the outcomes of the respective NICE guidance.

7.5 What unit costs were assumed? How were these calculated?

The costs of drugs were obtained from the most recent edition of the BNF[3] and are shown in Table 7.5). The annual treatment costs include outpatient visits which have been calculated using the Payments by Results tariffs for a hepatology outpatient follow-up attendance in 2005/2006. The number of visits is based on a clinical protocol outlined in Appendix 15 of Shepherd et al[55]. Costs are shown below.

Table 7.5: Estimated treatment costs.

Drug	Unit cost of drug (£, 2007)	Annual drug cost (£, 2007)	Annual outpatient visit cost (£, 2005/2006)[1]	Annual treatment cost (£, 2007)	Comments
Entecavir	378	4,599	1155	5,754	Drugs costs are based on 0.5 or 1 mg 30-tablet pack, one oral tablet taken daily.
Lamivudine	78.09	1,018	1155	2,173	Drugs costs are based on 100 mg 28-tablet pack, one oral tablet taken daily
Adefovir	315	3,833	1155	4,990	Drugs costs are based on 10 mg 30-tablet pack, one oral tablet taken daily
Telbivudine	290.33	3,785	1155	4,940	Drugs costs are based on 600 mg 28-tablet pack, one oral tablet taken daily
IFNα-2a	45.19	3,254	1155	4,409	Drugs costs are based on 9 million units, self-administered injection 3 times a week for 24 weeks
pegIFNα-2a	132.06	6,339	1680	8,019	Drugs costs are based on 180 μg syringe, self-administered injection once a week for 48 weeks

[1]Based on clinical protocol outlined in Appendix 15 of Shepherd et al.[55]. 11 outpatient visits are costed for all therapies except pegIFNα-2a where 16 visits are costed. Each outpatient visit was costed at £105.

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve day case or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Entecavir, like the other antivirals, is an oral regimen and is self-administered by patients at home. However, therapy should be initiated by a physician experienced in the management of CHB infection. No additional tests or investigations will be required beyond those already employed in routine clinical practice. No other therapies need to be routinely administered at the same time as entecavir as part of a course of treatment. Unlike the antivirals, IFNα-2a and pegIFNα-2a are administered as subcutaneous injections, three times weekly and once-weekly respectively, and are not as well-tolerated as the antivirals. Common side effects are influenza-like illness, fatigue, anxiety and depression.

In addition to drug costs, outpatient visits for entecavir have been calculated using the Payments by Results tariffs for a hepatology outpatient follow-up attendance in 2005/2006 (see Section 7.5).

7.7 Were there any estimates of resource savings? If so, what were they?

Analysis was conducted in relation to drug budget only. The cost-effectiveness section showed that entecavir is associated with reduced rates of liver-related complications and transplants, and therefore savings in non-drug resource use. However these savings could not be attributed to the first year of therapy and so were not included as off-setting savings to the budget impact of entecavir.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

8 Appendices

8.1 SmPC

8.2 Clinical Search Strategy

8.3 Clinical Systematic Literature Review Report

8.4 Network Meta Analysis Report

8.5 Economics Search Strategy

8.6 Data Tables of Cost Effectivenes Studies

8.7 Data Tables of QoL Studies

8.8 Sensitivity Analyses

8.9 Budget Impact Alternative Scenario Analysis

All appendices are provided in a separate electronic file.

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Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Elizabeth Boxall

Name of your organisation Association of Clinical Microbiologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) Consultant clinical scientist providing a diagnostic service for screening patients for suitability for treatment and for monitoring patients on antiviral therapy and checking for the development of resistance.

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Condition currently treated using interferon or antiviral drugs such as lamivudine or adefovir. Lamivudine monotherapy leads within 2 years to the development of resistance. More antiviral drugs are becoming available, accumulated clinical trail data needs to be reviewed to assess appropriate use.
Many sub groups – paediatric use is particularly important to get right. HBeAg positive and negative sub groups need to be considered.
Technology should be used initially in specialist centres
Must be clearly defined that these drugs are for the treatment of persistent infections and not acute infections.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
Clear treatment end points/outcomes are needed

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
This agent is not yet in use in clinical practice in the UK

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not yet aware of this clinical trail data

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I do not presently have access to this data

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NHS staff would need education, but as this drugs should only be use in specialist centre who have already carried out or are aware of the clinical trials this should not be a problem.
Resources for antiviral drug resistance investigation and assays would be required for patients who failed on therapy.

Clinical Expert Statement Template

Thank you for agreeing to give us a personal statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the place of the technology in current practice?

How is the condition currently treated in the NHS?

Chronic hepatitis B is treated with either standard, or pegylated interferon, or with lamivudine, or lamivudine in combination with adefovir, or with adefovir. Newer drugs include entecavir or telbivudine, and on the horizon, tenofovir.

Is there significant geographical variation in current practice?

Yes.

Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Yes; there are differences regarding for example the indications for treatment, the need for liver biopsy, the appropriate first-line therapeutic approach, the need for combination therapy in all patients, including those with lower levels of hepatitis B replication and the possibility of using an add-on therapeutic approaches.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Yes; patients with higher levels of replication may be at greater risk of developing resistance to a lineage of drugs. Patients with cirrhosis require more rapid intervention and careful monitoring. Patients with decompensated cirrhosis are not suitable for interferon treatment.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

By and large these treatments are applied in specialist clinics. Specialist nurses are increasingly involved in the management of patients with chronic hepatitis B. It is mandatory to utilise specialist nurses for the management of patients on interferon.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There is some variation in the application of these treatments, either as single agents or in combination. There is also some variation in the ability to prescribe newer agents which have not yet been assessed by NICE

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines have been published by the European Association for the study of the liver, the American Association for the study of the liver, the German Association for the study of the liver and the Asian Pacific Association for the study of the liver. Other clinical reviews have also been published which provide information.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The circumstances in which the trials were conducted do pertain to current UK practice.

What, in your view, are the most important outcomes and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Probably, the most important outcome is rapid HBV DNA suppression as this can lead to loss of HBeAg in HBeAg positive patients and is less likely to lead to resistance. The majority of patients will require long-term suppression. Serum aminotransferases usually improve once HBV DNA has been suppressed, and hepatic histology improves.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side-effect profile of new nucleoside therapies including entecavir and telbivudine are very different to those seen with interferon. By and large nucleoside analogues have few side-effects and are taken orally. It is possible that rare patients on telbivudine may have elevated creatinine phosphokinase (CPK) levels which can lead to myalgia or a myositis. These patients will need monitoring. A long-term post licensing monitoring program is in place to monitor the risk of carcinoma in patients taking entecavir. The major side effects of new nucleosides are flares in hepatitis as viral load decreases or increases. These are not usually problematic except in patients with cirrhosis who may decompensate.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK.
Is the technology easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its use?

The advantages of these new agents are more potent hepatitis B suppression, and if rapid DNA suppression occurs, lower rates of resistance. These agents are generally easy to use and will be acceptable by patients for that reason.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

This is an important question which has not yet been fully resolved it is thought that patients with active chronic hepatitis who show signs of progression should be treated. Patients who have very high levels of replication but are young and have minimal hepatitis can be monitored.

Any additional sources of evidence?

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There are well controlled registration clinical trials which provide this evidence. These peer reviewed papers have been published in authoritative journals.

Unfortunately the design of the some of these trials was not optimal which leaves open some questions regarding long-term suppression and rates of resistance. Treatment for one year is usually insufficient for the vast majority of HBeAg positive and HBeAg negative patients with chronic hepatitis B.

Implementation issues

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Resistance testing might be required. Longitudinal monitoring of hepatitis B DNA will be a fundamental requirement of the institution of this technology.

Please note: The NHS is required by the Department of Health and Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.
If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and Welsh Assembly Government to vary this direction.
Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

There are a number of well established laboratories and clinical units that can implemented the requirements of the likely guidance.

Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

[redacted]

Name of your organisation

Representing British Society for Gastroenterology

Are you (tick all that apply):

- I am a specialist in the treatment of people with the condition for which NICE is considering this technology?

What is the expected place of the technology in current practice?

Entecavir is:

- more potent than lamivudine, adefovir and telbivudine; more patients achieve HBV DNA negativity at 6mths and there is a more rapid decline in HBV DNA;
- significantly less likely to give resistance at 1, 2, and 3 years after starting treatment;
- is cheaper, in our hospital, than using a combination of lamivudine and adefovir.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice?

At [redacted] we have followed the current NICE guidelines which recommend for HBe antigen positive and negative cases that we offer a trial of pegylated interferon for up to 12 months and in those that fail to achieve a sustained response, we offer the following:

For those with HBV DNA > or = 10^7copies/ml:
either combined lamivudine 100mg and adefovir 10mg/day
or entecavir 0.5mg.

For those with HBV DNA < 10^7copies/ml:
Lamivudine 100mg and for those with an incomplete response (remaining detectable HBV DNA at 6 months) addition of adefovir 10mg.

Are there differences of opinion between professionals as to what current practice should be?

Some physicians will:
- not offer pegylated interferon, preferring to start with nucleos/tide therapy;
- give combination therapy to all viraemic patients from the start.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are two families of nucleos/tide analogues exhibiting cross resistance within each family but not between families.

Family 1 includes
- lamivudine (L);
- emtricitabine (available with tenofovir as truvada) (NL)
- telbivudine (L);
- entecavir (L).

Family 2 B includes:
- adefovir (L)
- tenofovir (NL).
- :

Entecavir is:
- more potent than lamivudine, adefovir and telbivudine, more patients achieving HBV DNA negativity at 6mths and a more rapid decline in HBV DNA;
- significantly less likely to give resistance at 1, 2, and 3 years after starting treatment;
- is cheaper than using a combination of lamivudine and adefovir.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with cirrhosis should not be given interferon but should start on the most potent nucleos/tide analogue with the lowest risk of developing drug resistance: at the moment this is entecavir.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Because of the danger of drug resistance, treatment is supervised from hospital Hepatology/GI Units.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Because of cost the uptake around the country is variable.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Best Practise in Rx of CHB: a summary of the European Viral Hepatitis Educational Initiative (EVHEI)
J Hepatology 2007 October 47 588-597.

The advantages and disadvantages of the technology

Entecavir has the advantage of having low resistance rates comparable to those seen with combination treatment with lam and adefovir. Although experience is limited to 3 years of therapy there have been few if any significant side effects. It should be born in mind however that therapy will need to continue for many years in most cases (Nowak et al 1996 PNAS 93 4398).
Resistance occurs more frequently if patients have had prior therapy with lamivudine; entecavir should therefore probably be used as first line therapy.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

In our hospital entecavir is the drug of first choice in those with high HBV DNA levels (10^7 or greater).

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The trials were conducted under conditions that allow extrapolation to UK patients with evidence of progressive disease (stage 1 or more fibrosis).

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The endpoint is rapid control of HBV replication as indicated by HBV DNA being undetectable by sensitive PCR.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

A tumour was found in rats but there has been no suggestion of similar problems in humans

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No.

Implementation issues

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This therapy is likely to add substantially to the cost of care of those with HBV liver diasease but Liaw et al (NEJM 2004 351 1521), using lamivudine , have shown that these anti-viral therapies significantly prolong life and are cost effective.
The therapy can be delivered, alongside therapy for HCV induced liver disease, in the developing Hepatology Networks. It is estimated that between 180,000 and 325,000 cases exist and around 30% of these will die of cirrhosis or HCC if untreated. These cases occur in ethnic minority groups.
Some patients will not require treatment if HBV DNA is undetectable or $<10^4$

Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Hepatitis B Foundation UK

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) X Co-ordinator /CEO
- other? (please specify)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

The advantage is that the drug will give those patients who have developed resistance to the other therapies a chance to live and not develop serious liver disease

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition as mentioned above
- physical symptoms reduces the physical symptoms
- pain helps reduce associated pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.) means patients can get back to work and live a normal life and contribute to society
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

All research in other EU countries shows the earlier an intervention is made with treatment the mors cost effective it is dealing with end stage liver disease is painful needless and expensive

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

As this is an oral therapy patients find it easy to use and comply
Reduces cost of expensive trips to hospital
The only concern is that some patients will develop resistance to this therapy
Which is why patients need as many choices as possible to overcome that problem

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.
No patients are very very pleased to a choice of therapies

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?
All patients might need this therapy

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

There are other oral therapies which many patients have developed resistance to This oral therapy is much better than having to self inject for 48 weeks as is the case with Peg-interferon

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall YES
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection) YES
- where the technology has to be used (for example at home rather than in hospital)USED AT HOME
- side effects (please describe nature and number of problems, frequency, duration, severity etc.) VERY FEW DIFFERENT FROM PATIENT TO PATIENT

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

No DISADVANTAGES

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.
YES IT DOES

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?
NOT TO THE KNOWLEDGE OF THIS PATIENT GROUP

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.
Euopean Orientation Towards the Better Management of hepatitis B in Europe
Recommendations of the Hepatitis B Expert Group
Chaired by Dr T Ulmer MEP

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Are there groups of patients that have difficulties using the technology?

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.