Sebivo® (telbivudine)

SINGLE TECHNOLOGY APPRAISAL (STA)

MANUFACTURER SUBMISSION OF EVIDENCE

List of Abbreviations

A&E	Accident and emergency
AASLD	American Association for the Study of Liver Diseases
AE	Adverse events
ALT	Alanine aminotransferase
APASL	Asia Pacific Association for the Study of Liver
AST	Aspartate aminotransferase
BSC	Best standard care
CC	Compensated cirrhosis
CDC	Centres for Disease Control
CHB	Chronic hepatitis B
CI	Confidence interval
CK	Creatine kinase
DCC	Decompensated cirrhosis
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
EMEA	European Medicines Evaluation Agency
ER	Emergency room
ESRD	End stage renal disease
ETV	Entecavir
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
ICER	Incremental cost effectiveness ratio
IFN	Interferon alfa
ITT	Intention to treat population
LAM	Lamivudine
LDT	Telbivudine
Mg	Milligram
NRTIs	Nucleoside Analogue Reverse Transcriptase Inhibitors
ns	Not significant
OR	Odds ratio
PCR	Polymerase chain reaction
PEG IFN	Pegylated Interferon

PI	Product information
QALY	Quality adjusted life year
RNA	Ribonucleic acid
RR	Relative risk
SD	Standard deviation
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal

Appendices Provided Separately from Main Submission

The appendices below are provided electronically on CD-Rom (separate from the main submission) to assist the Evidence Review Group with review of our submission and preparation of their report.

Appendix	Description of Content
A	Conducting a mixed comparison model between telbivudine and entecavir
B	Details of the distributions used in the viral load model.
C	Cox Proportional Hazards Model Derivation
D	Assumptions made in the construction of the viral load model
E	Difficulties encountered when replicating the model used in the HTA report
F	Details of the distributions used in the seroconversion model
G	Assumptions made in the construction of the seroconversion model
H	Annual Examination Costs
I	Costs of New Patient and Pre-treatment Evaluations
J	Results of the modelling
K	Comparison of the result from our replication of the HTA model and the results stated in the HTA report
L	Search strategy used for Section 5 (clinical effectiveness – indirect comparison)
M	Systematic Literature Review of Clinical Trials for Sebivo (from 1st January –September 2007)

Section A

1 Description of technology under assessment

1.1 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: Sebivo®

Approved name: Telbivudine

Therapeutic class: Antiviral for systemic use [ATC code: JO5AF11].

1.2 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 (for example, date of application and/or expected approval dates).

UK marketing authorisation was granted on 24th April 2007. Telbivudine (Sebivo®) was launched in the UK on 26th June 2007.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

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

1.4 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.

Current usage in the UK is limited to two sites that participated in the GLOBE study.

On-going studies include study 2406, a randomised, open-label, controlled, multi-centre two-year study comparing efficacy and safety of telbivudine in combination with peg-interferon alpha-2a with peg interferon alpha-2a monotherapy, and with telbivudine monotherapy in treatment naïve, HBeAg- positive CHB patients. The study includes 5 sites in the UK with a recruitment target of 15 patients over the 5 sites (currently 8 patients have been enrolled).

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

As of 24th April 2007, Telbivudine has received EMEA approval through the centralised approval procedure. Telbivudine has also regulatory approval in 76 countries outside of the EU/EEA. These countries are listed below:

Albania; Argentina; Aruba; Australia; Bahrain; Bangladesh; Belarus; Bosnia Herzegovina; Brazil; Cambodia; Canada; Chile; China; Colombia; Costa Rica; Croatia; Cuba; Curacao; Dominican Rep.; Ecuador; Egypt; El Salvador; Ghana; Guatemala; Honduras; Hong Kong; India; Indonesia; Ivory Coast; Jamaica; Japan; Kazachstan; Kenya; Kirgizia; Korea (South); Kosovo; Kuwait; Lebanon; Macau; Macedonia; Malaysia; Mexico; Moldovia; Morocco; New Zealand; Nicaragua; Nigeria; Pakistan; Palestine;

Panama; Peru; Philipines; Russia; Qatar; S. Korea; Serbia Montenegro; Singapore; Sri Lanka; Srpska; Sudan; Switzerland; Taiwan; Tanzania; Thailand; Trinidad & Tobago; Turkey; UAE; Uganda; United States; Uruguay; Uzbekistan; Venezuela; Vietnam; Yemen; Zambia, and Zimbabwe.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Novartis submitted to the Scottish Medicines Consortium (SMC) on the 1st of October. It is expected that SMC recommendation will be published on 11th of February 2008.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

A pack of telbivudine comprises 28 film-coated tablets each containing 600mg.

1.8 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

For adults, the recommended dose of Sebivo is 600mg (one tablet) once daily, taken orally, with or without food. Therapy must be initiated by a physician experienced in the treatment of chronic hepatitis B.

The optimal treatment duration is unknown. Treatment discontinuation should 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 at least 3-6 months apart) or until HBs seroconversion or loss of efficacy.
- In HBeAg-negative patients, treatment should be administered at least until HBs seroconversion or until there is evidence of loss of efficacy.

1.9 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.

£290.33 (excl. VAT) for 28 days.

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

Therapy must be initiated by a physician experienced in the management of chronic hepatitis B infection which in the UK usually will be in a secondary care setting, most commonly in a tertiary referral centre, on an outpatient basis.

1.11 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?

Available evidence does not support the use of telbivudine monotherapy in patients with

established lamivudine resistant Hepatitis B virus infection.

HBV DNA levels and liver function are measured as part of the normal management of CHB. Data suggests that measuring HBV DNA levels at week 24 may allows better tailoring of therapy to individual patient needs. Treatment decisions regarding continuing, switching to or adding on alternative treatments based on degree of viral suppression at this time point may lead to better (long term) outcomes. To date it has been shown that effective early viral suppression at week 24 predicts higher efficacy and lower resistance at 2 years [1, 2].

2 Statement of the decision problem

	Final Scope issued by NICE	Decision Problem addressed in the submission
Intervention(s)	Telbivudine alone or in combination with other therapies.	Telbivudine alone (There is not enough evidence in combination therapy and this indication is not within licence)
Population(s)	Adults with compensated liver disease and active chronic hepatitis B (that is evidence of viral replication and active liver inflammation)	As per final scope
Current standard comparators	• Interferon alfa-2a • Interferon alfa-2b • Peginterferon alfa-2a • Lamivudine • Adefovir dipivoxil • Entecavir	The intended comparator for this submission **is Lamivudine, first line oral antiviral treatment**.
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 • adverse effects of treatment	Need clarification on 'survival' - to be discussed at the meeting on 9 October 2007. Other outcomes as per final scope
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. 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. Costs will be considered from a NHS and Personal Social Services Perspective.	As per final scope

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 the Technology Appraisal No. 96, this STA will not specifically consider people with chronic hepatitis B 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. Guidance will be issued in accordance with the marketing authorisation.	The analysis considers HBeAg-positive and HBeAg-negative CHB patients with compensated liver diseases in two separate groups according to their differing characteristics, responses and outcomes. Current international clinical guidelines such as the American Association for the Study of Liver Disease (AASLD) and the Asia-Pacific Association for the study of the Liver (APASL) recommend treatment in CHB patients with elevated ALT (i.e. ALT ≥2 x ULN). This group of patients represent the majority of patients treated in the UK.
Related NICE recommendations	Related Technology Appraisals: NICE Appraisal Guidance No 96 - Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a (February 2006).	As per final scope

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission.

Hepatitis B is a potentially fatal liver disease caused by the hepatitis B virus (HBV). The majority (95%) of people who are infected as adults will recover spontaneously. The remaining 5% of patients will develop chronic hepatitis B (CHB) defined as viraemia and hepatic inflammation for more than 6 months (TA 96). It is estimated that about 325'000 people in the UK have CHB, with 7'700 new cases of CHB each year [3, 4]. Fifteen to forty per cent of infected patients will develop cirrhosis, liver failure and hepatocellular carcinoma (HCC). Patients with chronic hepatitis B are one hundred times more likely to develop hepatocellular carcinoma than those who are not infected [5], and 15% to 25% of CHB patients die because of these liver disease sequelae [6].

Due to its long-term complications, CHB has an important impact on the National Health Service (NHS). It has been estimated that the management of CHB in the UK could cost up to £375, rising to £429 million per annum, if time lost at work is included [7]. Worldwide, 500,000 to 1.2 million deaths per year are attributed to CHB-associated complications [8, 9].

The main goal of antiviral therapy for CHB is to suppress the level of virus (HBV DNA) for a prolonged period of time in order to reduce the risk of disease progression and HCC, and also to improve long term health outcomes. There is a growing body of evidence indicating that HBV DNA viral load is the key marker for disease management and also helps predict clinical outcomes. Additional goals include HBeAg seroconversion and, over the longer term, histologic response. ALT is also measured but interpretation is hampered by fluctuations not necessarily related to HBV. Current therapy aims at inhibiting viral replication and achieving remission of hepatic disease, but either significant toxicity (such as that seen with PEG-IFN and IFN) or emergence of resistance to anti-viral nucleoside/nucleotide therapies can limit long-term efficacy of available treatments.

Consequently, there is still an unmet need in the treatment of CHB. Newer agents are required that will achieve rapid and profound viral suppression, thereby resulting in higher rates of seroconversion and ALT normalisation and lower rates of resistance than lamivudine, whilst remaining as safe, well tolerated and convenient to administer over the long term. This submission demonstrates the clinical benefits and cost-effectiveness of telbivudine in patients with compensated CHB. Telbivudine 600mg daily has been shown to be a more effective and potent therapy for CHB than lamivudine in terms of therapeutic response, HBV DNA suppression, HBeAg seroconversion, ALT normalisation and histologic response. In addition, it has a similar safety profile to lamivudine, and therefore represents a superior first-line oral antiviral treatment for CHB compared with lamivudine. Consequently, telbivudine represents a cost-effective use of NHS resources and addresses an unmet clinical need for a more effective, well tolerated treatment with lower resistance rates for patients with CHB.

- The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.

Sebivo® (telbivudine)

Telbivudine received EU marketing authorisation on 24 April 2007, based on the 1 year results of the pivotal GLOBE study, and has been marketed in the UK since 26th June 2007.

Telbivudine, is a synthetic thymidine nucleoside analogue with activity against HBV deoxyribonucleic acid (DNA) polymerase. As such it may be compared with other nucleoside/nucleotide analogues including lamivudine, adefovir dipivoxil and entecavir.

- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.

Sebivo is available in packs of 28 film-coated tablets containing 600 mg telbivudine per tablet. The UK list price is £290.33 (excl. VAT) per pack of 28 tablets.

Treatment of chronic hepatitis B is ongoing.

- The indication(s) and any restriction(s).

Indication

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

It is expected that telbivudine will be prescribed as a first line oral therapy for chronic hepatitis B in patients who are unwilling or unable to tolerate treatment with interferons.

Restrictions/special precautions

Due to the limited data available, telbivudine should be used with caution in cirrhotic patients. These patients should be closely monitored for clinical, biochemical and virological parameters associated with hepatitis B during treatment and after treatment is discontinued.

There are no efficacy and safety data in patients with decompensated cirrhosis. Telbivudine is not indicated in patients with decompensated cirrhosis, although a study is ongoing (see Section 2.2.5).

Available evidence does not support the use of telbivudine monotherapy in patients with established lamivudine resistant hepatitis B virus infection.

The safety and efficacy of telbivudine in liver transplant recipients are unknown.

Telbivudine has not been investigated in co-infected hepatitis B patients (e.g. patients co-infected with human immunodeficiency virus [HIV], hepatitis C virus or hepatitis D virus), although a study in co-infected HIV patients is planned (see Section 2.2.5). Telbivudine does not have activity against HIV *in vitro*.

Telbivudine is not recommended to be used in combination with lamivudine. In a phase II study (study NV-02B-010), the treatment response observed with combination therapy of telbivudine and lamivudine was lower than with telbivudine alone.

There are currently no efficacy and safety data for other antiviral combinations with telbivudine, although a combination study with pegylated interferon is ongoing, as are 2 combinations studies with adefovir dipivoxil (see Section 2.2.5).

- The recommended course of treatment.

Treatment of chronic hepatitis B is usually ongoing, and the optimal treatment duration is unknown. Treatment discontinuation with telbivudine should 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 at least 3-6 months apart) or until HBs-seroconversion or loss of efficacy.
- In HBeAg-negative patients, treatment should be administered at least until HBs-seroconversion or until there is evidence of loss of efficacy.

- The main comparator(s).

Lamivudine, a nucleoside analogue, is currently the most widely used first-line oral-antiviral for the treatment of patients with CHB. Lamivudine 100mg daily was used as the active comparator in the registration study for telbivudine.

Entecavir, another nucleoside analogue, is the most recent oral antiviral agent for CHB to be licensed in the UK. It is not widely used first-line due to cost, but is of interest due to the claimed low rates of resistance. The phase III studies for entecavir were also conducted using lamivudine as the active comparator. There are no head to head data for telbivudine and entecavir.

- Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.

The key clinical evidence in this submission comes from a 104-week, full ITT (intention to treat), randomised, double-blind, double-dummy trial comparing telbivudine with the active comparator and current standard of care, lamivudine, in nucleoside-naïve patients with compensated chronic hepatitis B [10].

At the request of NICE, an attempt has been made to conduct an indirect comparison between entecavir and telbivudine, using the registration studies for both agents with the common comparator lamivudine (see Section 2.6 and Appendix A).

- The main clinical results of the randomised trials and any relevant non RCTs.

GLOBE Trial (Study 007) – Intention-to-Treat (ITT) Population

The key clinical evidence in this submission comes from a 104-week, full ITT (intention to treat), randomised, double-blind, double-dummy trial comparing telbivudine with the active comparator and current standard of care, lamivudine, in nucleoside-naïve patients with compensated chronic hepatitis B (GLOBE study NV-02B-007). This study in 1367 evaluable patients (921 HBeAg-positive; 446 HBeAg-negative) is the largest conducted in CHB to date. The GLOBE study compared the clinical efficacy, safety and tolerability of telbivudine (600mg) with lamivudine (100mg). The primary efficacy endpoint for Study 007 measured at weeks 52 and 104 was a composite serologic endpoint "Therapeutic Response" defined as suppression of HBV DNA to <5 $\log_{10}$ copies/mL plus e*ither* clearance of detectable HBeAg *or* ALT normalisation. Full results from this trial are presented in section 5.4.

The key findings of the GLOBE study can be summarised as follows:

- **Therapeutic response:** In the HBeAg-positive ITT patient population, telbivudine had significantly superior efficacy compared with lamivudine at year 1 and year 2 in the primary composite efficacy endpoint of "therapeutic response". For HBeAg-negative patients, the therapeutic response for telbivudine was non-inferior at year 1 and statistically superior at year 2.

- **HBV DNA suppression:** HBV DNA suppression was statistically superior for telbivudine compared with lamivudine for both HBeAg-positive and HBeAg-negative patients at year 1 and 2. There were also a significantly higher proportion of patients with undetectable HBV DNA levels (i.e. PCR negative) at year 1 and year 2 for the telbivudine cohort compared with lamivudine.

- **e-antigen response:** HBeAg-positive patients demonstrated similarity at 1 year in proportions of patients experiencing HBeAg loss, e-seroconversion or virologic response, although there was a numerical difference in favour of telbivudine. At year 2, e-seroconversion was still numerically greater for telbivudine patients.

- **ALT normalisation:** ALT normalisation at year 1 was similar for telbivudine and lamivudine patients. In HBeAg-positive patients, there was a statistically significant difference in favour of telbivudine in the proportion of patients achieving ALT normalisation at 2 years.

- **Histologic response:** At year 1 the histologic response was statistically significantly better for HBeAg-positive patients treated with telbivudine compared with lamivudine; histological responses in HBeAg-negative patients at 1 year were similar for both compounds. Due to the invasive nature of the procedure, biopsies were not taken at year 2.

- **Genotypic resistance:** For both HBeAg-positive and HBeAg-negative patients, telbivudine showed significantly less emergence of genotypic resistance than lamivudine after 1 and 2 years of treatment.

- **Efficacy in ALT 2xULN group:** For the 70% of patients currently recommended for treatment according to international guidelines (on the basis of elevated ALT to twice upper limit of normal range), telbivudine demonstrated significantly higher HBeAg seroconversion rates than lamivudine (HBeAg-positive patients only).

015 Study- Phase III trial in China

This randomised, double-blind, Phase III trial enrolled patients with compensated CHB at 18 sites in China. The ITT analysis comprised data from 332 patients (290 HBeAg-positive and 42 HBeAg-negative) who had received 600 mg/day telbivudine or 100 mg/day lamivudine for up to 2 years [11].

At Week 52, telbivudine resulted in a significantly greater decrease in HBV DNA from baseline (the primary efficacy endpoint) compared with lamivudine. Telbivudine treatment was also significantly more effective than lamivudine for the proportion of patients achieving PCR non-detectable HBV DNA, therapeutic response, ALT normalisation, and HBeAg loss.

Safety and Tolerability

Results obtained in the Week 104 GLOBE analysis support an overall favourable safety profile for telbivudine versus lamivudine. During the GLOBE trial, serious adverse events were infrequent, occurring in only 5.6% of patients overall (4.9% of telbivudine recipients vs. 6.4% of lamivudine recipients). Adverse events reported for telbivudine were generally mild and transient, with a comparable adverse event profile to that of lamivudine. The majority of patients in both treatment groups reported at least one adverse event (81% in the telbivudine group vs 77% in the lamivudine group), but less than one-third of adverse events were considered attributable to study drug and few gave rise to study discontinuation (0.7% telbivudine:1.5% lamivudine).

Full discussion on adverse events can be found in section 5.7.

Economic Evaluation

Our estimate of the cost-effectiveness of telbivudine compared with lamivudine in CHB (see section 6) is based on data from the subgroup of GLOBE patients meeting international criteria for treatment (i.e. ALT elevated > 2 x ULN).

Two models are provided; a seroconversion model and a viral load model. The seroconversion model replicates the approach used in the previous NICE assessment and is applicable only to HBeAg-positive patients. The viral load model simulates both patients with HBeAg-positive disease and those with HBeAg-negative disease. The viral load approach is our favoured methodology however we have attempted to replicate the seroconversion model that provided data for the previous NICE assessment so that the results produced by the two methodologies can be compared.

For the viral load model, in HBeAg-positive patients, the mean incremental cost-efectiveness ratio (ICER) is between £9,332 and £14,665; for HBeAg-negative patients, it is between £10,497 and £33,300.

For the seroconversion model (HBeAg-positive patient only), the ICER for the treatment algorithm of telbivudine followed by best supportive care is £13,193 (95% CI £7,778-£25,194); for telbivudine followed by adefovir followed by best supportive care, the ICER is £15,684 (95% CI £9,491 - £28,151).

Budget Impact

It is important to stress that robust data on incidence of hepatitis B and prevalence of CHB are scarce and might not reflect the current situation. Equally, it is difficult to determine the proportion of patients who are treated. In England and Wales, it has been assumed that 700 patients per year would be identified as eligible for treatment, based on the HTA report [12]. If all 700 patients were treated with telbivudine, followed by adefovir followed by best supportive care, it is expected that the upper bound of the budget impact would be £5 million per annum. In practice, it is expected that the numbers of patients treated would be fewer than 700 and, hence, the budget impact would be reduced.

Summary

These results demonstrate the clinical benefit and cost-effectiveness of telbivudine in patients with compensated CHB. As a consequence, telbivudine represents a cost-effective use of NHS resources and addresses an unmet clinical need for more effective treatments for patients with CHB.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Hepatitis B is a potentially fatal liver disease caused by the hepatitis B virus (HBV). The majority (95%) of people who are infected as adults will recover spontaneously. The remaining 5% of patients will develop chronic hepatitis B (CHB) defined as viraemia and hepatic inflammation for more than 6 months (TA 96). Latest estimates suggest that about 326'000 people in the UK have CHB, almost double the figure from five years ago [3]. Current prevalence and incidence may be an underestimate of the problem since neither measure takes into account the impact of recent migration into the country.

Fifteen to forty per cent of infected patients will develop cirrhosis, liver failure and hepatocellular carcinoma (HCC). Patients with chronic hepatitis B are one hundred times more likely to develop hepatocellular carcinoma than those who are not infected [5], and 15% to 25% of CHB patients die because of these liver disease sequelae [6].

Due to its long-term complications, CHB has an important impact on the National Health Service (NHS). It has been estimated that the management of CHB in the UK could cost between £26 and £375 million per annum, rising to £429 including time lost at work [7].

Worldwide, 500,000 to 1.2 million deaths per year are attributed to CHB-associated complications [8, 9]. Mortality data specific to the UK are scarce. In England and Wales, only one publication provides a measure of the risk associated with CHB and HCC mortality in men, and liver disease mortality in both women and men [13]. The mortality rate of males carrying HBsAg was 26 times that of the general population. Non-malignant chronic liver disease accounted for 12.4% of deaths in the cohort studied; this was higher than deaths from lung cancer (11.9%). It should also be borne in mind that the cause of death may be registered as HCC, liver failure, etc, and not CHB *per se*.

The costs associated with the management of CHB and its sequelae have been estimated in several European countries, including the UK [14]. The average cost by disease state was found to increase across the identified disease states reflecting disease progression. Average annual disease state costs per patient were as follows (2001):

DISEASE STATE	COST in £ for 2001
Chronic hepatitis B	1'978
Compensated cirrhosis	2'208
Decompensated cirrhosis	8'821
Hepatocellular carcinoma	9'312
Transplantation	47'153
First year post-transplant	16'157
Post-transplant	10'085

Modified from Brown et al, J Clin Gastroenterol, 2004

HBV is a small DNA virus which has an outer protein coat (hepatitis B surface antigen, HBsAg) and an inner protein core (hepatitis B core antigen, HBcAg). In infected hepatocytes, HBcAg is produced in excess and during release from the cells it is cleaved to produce the hepatitis B e antigen (HBeAg). Patients expressing HBeAg are termed HBeAg-positive patients. There is a form of HBV which does not cause infected cells to secrete HBeAg, and patients with this form of virus are termed HBeAg-negative patients [15].

The distinction between HBeAg-positive and negative patients is important because the patient populations differ in several demographic respects and treatment approaches and outcomes vary. Nonetheless, in both types of patients, viral suppression and prevention of end stage liver disease are the goals of antiviral therapy, as is the prevention of disease progression.

CHB is thus a disease that not only has serious consequences for the patient but has a considerable impact on health care resources. Thus effective treatment of the disease resulting in undetectable levels of HBV DNA, seroconversion or stabilisation aims to prevent clinical deterioration, as well as the associated co-morbidities and costs.

CHB treatment

Current therapy aims at inhibiting viral replication and achieving remission of hepatic disease, but either significant toxicity (such as that seen with PEG-IFN and IFN) or emergence of resistance to anti-viral nucleoside/nucleotide therapies can limit long-term efficacy of available treatments.

The treatment goals for CHB have been defined and can be summarised as follows:

1. Stop or reverse the progression of liver disease, thereby preventing subsequent development of cirrhosis and associated complications of liver failure;
2. Prevent the development of hepatocellular carcinoma;
3. Eliminate infectivity and transmission of hepatitis B to others.

Although treatment objectives are well established, treatment endpoints are not yet clearly defined and differ between HBeAg-positive and -negative patients. Whilst surface antigen-loss (HBsAg seroconversion) is the ideal outcome in both types of disease, in practice it is difficult to achieve. In HBeAg-positive patients, achieving sustained HBV DNA reduction, ALT normalisation, as well as loss of HBeAg and durable seroconversion over the longer term are critical. In HBeAg-negative patients, sustained

reduction in HBV DNA and ALT normalisation are the desired goals.

Undetectable HBV DNA levels facilitates HBeAg seroconversion and leads to reduction of ALT and thus viral load suppression is key for both HBeAg-positive and -negative individuals.

There are two major groups of therapies that are currently prescribed:

1) *Compounds that act on the immune system*

interferon (IFN)-based therapies such as IFN α-2b or pegylated IFN α-2a (PEG-IFN)

2) *Anti-viral compounds*

nucleoside/nucleotide analogues such as lamivudine, adefovir, and entecavir.

(i) IFN-α acts on the immune system to elicit broad antiviral activities. This compound has been used for many years, but has demonstrated limited success in suppressing HBV replication, with an estimated efficacy of only 37% [16]. IFN-α2b decreases serum HBV DNA levels, normalises aminotransferases and induce HBeAg seroconversion in no more than 25% of patients [17]. Interferon therapy is associated with frequent and systemic adverse events, limiting its use [18]. **Pegylated IFN** has been shown to be effective both when used alone and in combination with lamivudine in clinical trials, although the addition of lamivudine did not increase the HBeAg seroconversion rate compared with peginterferon alfa-2a alone [19, 20]. As with standard IFN, the proportion of responders to PEG-IFN is low (seroconversion rates of 25% and 35%, respectively) (TA96) and the response is not always sustainable.

(ii) Lamivudine is effective at suppressing HBV replication and decreasing hepatic pathology in HBeAg-positive and -negative CHB patients, including those who have failed to respond to IFN treatment (Hache and Villaneuve, Expert Opinion Pharmacother 2006). Chronic HBV-infected patients treated with lamivudine experience ALT normalisation in 72% of cases, whilst 98% show a significant decline in serum HBV DNA and 16% experience HBeAg seroconversion [21]. Unfortunately, resistance to lamivudine develops in 14 – 32% of patients after 1 year of treatment and in up to 60-70% of patients after 5 years [16].

(iii) Adefovir dipivoxil inhibits HBV replication in compensated liver disease and is also effective in lamivudine-resistant patients [22, 23]. After 48 weeks of treatments, more patients receiving adefovir dipivoxil had an improvement in histologic abnormalities, undetectable serum HBV DNA, and ALT normalisation compared with placebo. The rate of development of resistance to adefovir dipivoxil has been reported to be 3% after 2 years and 28% after 5 years [23]. Adefovir tends to suppress viral replication more slowly than other anti-virals. Moreover, a small proportion of patients may not respond at all to adefovir dipivoxil, seemingly related to polymorphisms at the HBV genome which compromise adefovir dipivoxil activity [24, 25].

(iv) Entecavir shows more potency in suppressing serum HBV DNA compared with lamivudine [25]. Entecavir resistance mutations have been reported in patients with prior lamivudine resistance, but only rarely in drug-naïve patients [26]. The rates of treatment emergent resistance to entecavir at 1 year are reported as less than 1%, however development of resistance after the first year has not been systematically determined [27].

In summary, despite existing therapy, many patients fail to develop durable virologic responses to currently available therapies due to suboptimal efficacy, poor tolerability or emergence of viral resistance.

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

Therapy for CHB has made considerable advances in the last decade, however results of current treatment are still unsatisfactory in several respects.

The main unmet needs in medical therapy of CHB are for agents that will rapidly achieve profound viral suppression, thereby resulting in higher rates of seroconversion and ALT normalisation and lower rates of resistance than lamivudine, whilst remaining as safe, well tolerated and convenient to administer over the long term.

Telbivudine was developed to improve therapy in these respects versus the current standard of care, lamivudine, and thus may be expected to improve long-term outcomes in CHB.

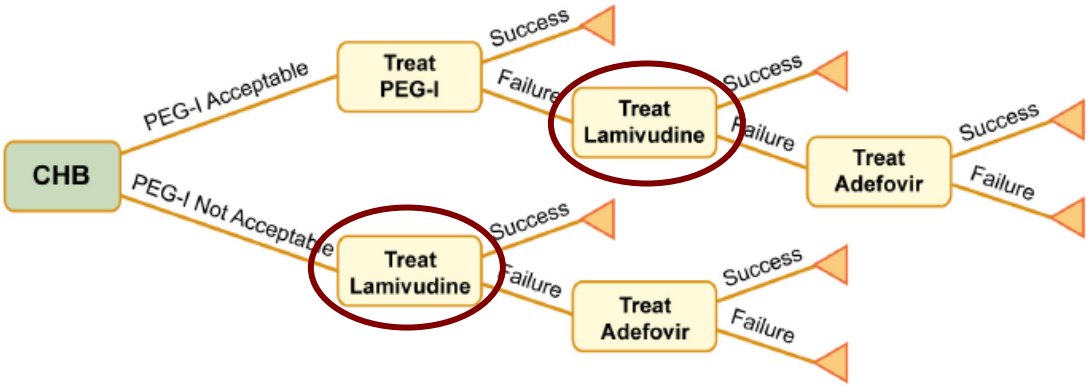
4.3 What is the principal mechanism of action of the technology?

Telbivudine is a potent inhibitor of HBV DNA replication. This synthetic thymidine nucleoside analogue expresses activity against HBV deoxyribonucleic acid (DNA) polymerase. It is efficiently phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours in the human hepatocarcinoma cell line, HepG2. Telbivudine-5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) and thus HBV replication. This inhibition is thought to involve competition with the natural substrate thymidine 5'-triphosphate and incorporation of telbivudine into viral DNA, causing DNA chain termination. Telbivudine is an inhibitor of both HBV first-strand (EC_{50} = 0.4-3.1 μM) and second-strand (EC_{50} = 0.12-0.47 μM) synthesis, and shows a distinct preference for inhibiting second-strand production. By contrast, telbivudine-5'-triphosphate at concentrations up to 100 μM did not inhibit human cellular DNA polymerases α, β, or γ. In assays relating to human mitochondrial structure, function and DNA content, telbivudine lacked an appreciable toxic effect at concentrations up to 10 μM and did not increase lactic acid production *in vitro*.

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

Technology appraisal guidance from the National Institute for Health and Clinical Excellence (NICE) for the use of peginterferon and adefovir dipivoxil (adefovir) for treatment of CHB are presented in Figure 2. The guidelines recommend a stepped care process whereby interferon or peginterferon is offered first, followed by lamivudine in those who fail the interferon treatment either because of lack of efficacy or tolerability, and finally use of adefovir in those who fail lamivudine [4]. This guidance is supported by the results of a cost-effectiveness treatment sequence model.

Figure 1: UK NICE-recommended treatment sequence



Telbivudine is intended for use for those patients eligible for Lamivudine treatment (in Figure 1 place of Telbivudine is circled)

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There is strong evidence that the risk of progression to cirrhosis and liver failure increases with higher serum levels of HBV DNA [28-30]. Significant improvements in PCR technology currently allow accurate and sensitive detection of HBV DNA down to levels as low as 50 copies/ml or lower (Taqman). This has allowed exploration of the link between profound viral suppression with new antivirals such as telbivudine and the more conventional treatment outcomes such as seroconversion or ALT normalisation. In this context, a key goal of CHB treatment is increasingly viewed as attainment of rapid and profound viral suppression, with serum HBV DNA as the key practical, early marker of antiviral efficacy to prevent long-term complications regardless of HBeAg status [1, 31]. HBV DNA suppression is a relevant marker for both HBeAg-positive and HBeAg-negative patients.

HBeAg seroconversion is clearly still an important treatment goal, as reflected in guidelines (AASLD, APASL, EASL) and in NICE TA96. It is also highly relevant to assessments of cost effectiveness because it suggests the potential for treatment discontinuation if seroconversion is sustained. However, because it can only be applied to HBeAg-positive patients, it's use in the overall patient pool is limited.

We would therefore propose that both HBV DNA suppression and seroconversion should both be taken into consideration when evaluating the clinical and cost-effectiveness outcomes of new therapies. This possible variation in preferred surrogate marker is addressed in a second cost-effectiveness model that analyses costs and outcomes in HBeAg-positive patients using seroconversion as a surrogate marker linked to long-term CHB disease outcomes.

There is currently uncertainty the use of combination treatment and the optimal time of its initiation. At present, there is no data for the use of telbivudine in combination with any other oral antiviral or with interferon (SPC). A phase II study (NV 003) explored

telbivudine and lamivudine as monotherapies or in various combinations in 104 HBeAg positive CHB patients. While telbivudine demonstrated superior antiviral activity and improved ALT normalisation, there was no additional clinical benefit observed as a result of adding lamivudine 100mg/day to telbivudine at 400 or 600mg/d [32]. A further trial (CLDT-600a-2406) is investigating the use of telbivudine in combination with Peg-IFN. Results are not expected for a further 2-3 years.

4.6 Provide details of any relevant guidelines or protocols.

In February 2006, NICE issued technology appraisal guidance on the use of adefovir dipivoxil and PEG-IFN α-2a for the treatment of CHB in the UK (revision was due in February 2007). The guidance states that PEG-IFN α-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 *(i.e. first line use).* In addition, the NICE guidance refers to the use of lamivudine second-line and recommends adefovir dipivoxil after lamivudine use, either alone or in combination with lamivudine when treatment with lamivudine has resulted in viral resistance [4].

The three major liver disease organisations – the American Association for the Study of Liver Diseases (AASLD), the Asian-Pacific Association for the Study of the Liver (APASL), and the European Association for the Study of the Liver (EASL) have each developed Practice Guidelines (AASLD) or issued Consensus Statements (APASL and EASL) regarding the management of chronic hepatitis B.

AASLD Practice Guideline -- Chronic Hepatitis B
The AASLD Practice Guidelines, recently updated, recommend that [16] www.aasld.org:

- HBeAg-positive patients with HBV DNA >20,000 IU/mL and ALT >2 x ULN are observed for 3 months and if no spontaneous HBeAg loss occurs they may receive treatment with any of the 6 FDA-approved anti-viral agents: this includes lamivudine and telbivudine although PEG-IFN α-2a, adefovir or entecavir are stated as preferred options. Pegylated interferon is recommended for 48 weeks while oral antivirals should given for a minimum of 1 year and be continued for 6 months after eAg seroconversion.

- HBeAg-negative patients with HBV DNA >20,000 IU/mL and ALT >2 x ULN, treatment may be initiated with any of the 6 FDA-approved anti-viral agents: this includes lamivudine and telbivudine although PEG-IFN α-2a (48 weeks), adefovir or entecavir are stated as preferred options. Oral antiviral treatments should be continued until patients have achieved HBsAg clearance.

EASL International Consensus Conference on Hepatitis B

EASL guidelines were published in 2003 [33], prior to the introduction of telbivudine, and are due to be updated in Q3/4 2007. At present they recommend treatment for patients with sustained increases in ALT >2 x ULN and serum HBV DNA >10^5 copies/mL as follows:

- HBeAg-positive moderate or severe CHB without cirrhosis: IFN for 4 to 6 months, or if contraindicated or if the patient fails to respond, lamivudine or adefovir for at least 1 year (4-6 months after virologic response)
- HBeAg-negative moderate or severe CHB without cirrhosis: IFN for 12 to 24 months, or if contraindicated or the patient fails to respond, lamivudine or adefovir for at least 1 year. The optimum duration of therapy is not known, but can be estimated from histological improvement due to sustained suppression

Asian-Pacific Consensus Statement on the Management of Chronic Hepatitis B:

APASL guidelines [34] recommend treatment for patients with active HBV replication (HBeAg and/or HBV-DNA positive >10^5 copies/mL) and ALT ≥2x ULN on two occasions with at least 1 month between observations, as follows:

- For HBeAg-positive patients without hepatic decompensation and ALT levels between 2 and 5 x ULN, 4 to 6 months therapy with IFN or PEG-IFN α-2a, or a minimum of 1 years treatment with lamivudine or adefovir
- For HBeAg-negative patients with intermittent or persistent increases in ALT, moderate to severe inflammation and serum HBV DNA >10^5 copies/mL, a 12-month course of IFN or PEG-IFN α-2a, with lamivudine or adefovir as less preferred options

It is anticipated that telbivudine will be prescribed according to the above guidelines and thus treatment will be initiated in patients with active HBV replication (HBeAg and/or HBV-DNA positive >10^5 copies/mL) and ALT ≥2x ULN.

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head–to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Overview

The systematic literature search was conducted to identify all relevant clinical literature involving the treatment of chronic hepatitis B with the antiviral treatments telbivudine, lamivudine or adefovir. In particular, the aim was to identify all relevant randomised trials that directly compared telbivudine and lamivudine.

In January 2007, literature searches were conducted using the Medline, EMBASE, Cochrane and Novabase (eNova) databases. Clinical trial registries were searched (US National Institutes of Health and the Australian Clinical Trials Registry). A US registry was used because UK registries are not available and the former are comprehensive data sources. An examination of the telbivudine registration dossier (in particular, the

Summary of Clinical Data) and other “in house” trials were undertaken in addition to a manual search of relevant publications.

Peginterferon alfa-2a and interferons alfa-2a and alfa-2b were not included in the search strategy because telbivudine is proposed as a first-line oral antiviral treatment, not as an alternative to PEG-INF. The interferons have immunomodulatory activity and, although they provide some antiviral activity, this is less than provided by nucleosides or nucleotides.

Exact details of the search strategy used for the retrieval of clinical evidence, including the specific databases searched, the date the searches were conducted and the date span of the searches, are provided in Appendix L.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Please see appendix L for the literature search carried out from 1st January to September 2007. This search identified no further RCT’s.

A total of 769 unique citations were identified during the search conducted on the Medline, EMBASE and Cochrane databases (after the removal of duplicates). For the trial registries and the eNOVA database, twenty two citations and seven citations were identified respectively.
Five relevant citations were retrieved for inclusion following the search of the Medline, EMBASE and Cochrane databases and six citations were retrieved from the eNOVA database (abstracts of relevant randomised trials) (eleven in total). No relevant randomised trials were retrieved from the search of the trial registries. The consolidated number of citations of direct randomised trials retrieved (after removing exact duplicates across the different databases) was seven, two of which were included as they were published direct randomised trials.
The breakdown of the number of citations identified from other sources is as follows. Five direct randomised trials were identified from the search of the telbivudine TGA registration dossier as being relevant for potential inclusion in the submission, two further abstracts of a relevant randomised trial were retrieved from the manual search and one “in house” trial was identified.

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

The reasons for excluding certain trials from further detailed assessment in the submission are provided in

Table 1. In summary, Study 003 and Study 010 were excluded as they were both Phase IIb trials (Study 010 was an extension study of Study 003). Consequently these trials have been superseded by Studies 007, 015 and 019 which are larger, more rigorous Phase III trials. Data collected from Study 003 and Study 010 were used for planning the Phase III trials. In addition, Study 003 included small patient numbers (104 patients were randomised equally across 5 treatment arms).

Table 1: Reasons for excluding each trial from further detailed assessment

Trial ID	Ground(s) for seeking exclusion	Details
Quality of the trial		
Study 003	• **Phase IIb trial:** preliminary data from this trial were used for planning the phase III trial, and Study 003 consequently has been superseded by Study 007. • Small patient numbers: 104 patients were randomised in a 1:1:1:1:1 ratio across 5 treatment arms. This resulted in only 19 and 22 patients in the lamivudine 100 mg and telbivudine 600 mg treatment groups, respectively.	Lai et al, 2005 [32], page 530 Lai et al, 2005 [32], page 258 & 531
Study 010	• **Phase IIb extension study** (of Study 003): the secondary objective of this trial was to gather preliminary data regarding the clinical efficacy of the drugs (telbivudine, lamivudine/telbivudine combination) compared to lamivudine monotherapy, prior to obtaining data from Phase III clinical trials. Again, as for Study 003, Study 010 has been superseded by Study 007. • The study was not powered for its endpoints (maintenance of clinical benefits in Study 003 in the longer term) as Study 003 was originally intended as a 52 week trial and no adjustments could be made to the sample size to accommodate loss of patients in the extension study. • Small patient numbers: the sample size was too small to demonstrate that the differences in efficacy between the drugs that were observed in the study achieved statistical significance.	Study 010 Synopsis, page 1 Study 010 Synopsis, page 4 Study 010 Synopsis, page 4
Outcomes reported in the trial		
Study 003	• Primary outcome of the trial was designed to compare the antiviral effects of two doses of telbivudine (400 mg/day vs 600 mg/day).	Study 003 Synopsis, page 1

Exclusion criteria are listed at the end of this submission in an additional Appendix (L).

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this. Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1. Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Four direct randomised clinical trials have been selected for inclusion in the submission, namely Study 007, Study 015, Study 007/015, Study 018 and Study 019 (See Figure 2 All of these trials include a direct comparison of telbivudine with the relevant comparator, lamivudine.

Table 2: Direct randomised trials selected for inclusion

Trial	Reports	Randomised treatments	Patient numbers
Study 007 (GLOBE)	Phase III, randomised, double-blind, multicentre, controlled , ITT ***Published as:*** • Lai et al, Telbivudine (LDT) vs. lamivudine for chronic hepatitis B: First-year results from the International phase III globe tribal, *Hepatology*, 2005, 748A • Lai et al, Maximal early HBV suppression is predictive of optimal virologic and clinical efficacy in nucleoside-treated hepatitis B patients: Scientific observations from a large multinational trial. (The globe study), *Hepatology*, 2005, 232A	Telbivudine versus Lamivudine in HBeAg positive and HBeAg negative patients	N=1,367 included in the ITT analysis (N=1,376 patients enrolled)
Study 015	Phase III, randomised, double-blind, multicentre, ITT ***Published as:*** • Hou et al, Hepatology 2006	Telbivudine versus Lamivudine	N=332
Study 018	Phase IIIb randomised, controlled, multicentre, open-label ***Published as:*** • Chan HL et al, Annals of Internal Medicine 2007	Telbivudine versus Adefovir dipivoxil, and effects of switching from Adefovir to Telbivudine, in HBeAg positive patients	N=135
Study 019	Phase IIIb, randomised, double-blind, multicentre ***Published as:*** • Hwang et al. APASL	Switching Antiviral Therapy from Lamivudine to Telbivudine versus Continued Lamivudine	N=246

As described in section 5.2.1 there is only one study, (007, GLOBE) that compares telbivudine with lamivudine that is relevant for this appraisal. Results from 52 weeks have been accepted for publication in NEJM (Lai et al) whilst the full results are contained in the Clinical Study Report from 104 weeks (104 wk CSR). For consistency, this submission uses the 104 wk CSR, unless otherwise stated. Given that only one study has been identified, it is not possible to present a QUOROM statement flow.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

There are no non-randomised controlled trials that are relevant to the decision problem.

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.

There are several ongoing clinical trials for telbivudine and these studies are summarised in the table below:

Study Number	Details
NV-02B-011 (CLDT600A2301)	Randomised, double-blind, controlled, Phase III study in adults with decompensated chronic hepatitis B and cirrhosis. Enrolment is complete. LPLV estimated December 2009.
NV-02B-022 (CLDT600A2303)	Global, multi-center study designed to allow for open label, longer term dosing with Telbivudine for CHB patients who have successfully completed a previous Phase IIb, III, or IIIb clinical trial in the telbivudine clinical development program, regardless of previous treatment assignment. LPLV estimated December 2009.
NV-02B-022A (CLDT600A2303A)	Open-label sub-study on telbivudine plus adefovir in adults with chronic hepatitis B previously treated in study NV-02B-022 and who met criteria for lack of efficacy on telbivudine. Recruitment ongoing.
NV-02B-029	Prospective, randomised, blinded trial of switching antiviral therapy from adefovir to the combination of telbivudine plus adefovir vs continued adefovir in adults with HBeAg- positive chronic hepatitis B and suboptimal viral suppression (PROACTIV Study)
NV-02B-031	Phase I pediatric pharmacokinetic study. Completed.
CLDT600A2406	Randomised, open-label, controlled, multi-center two-year study comparing efficacy and safety of telbivudine in combination with peg interferon alpha-2a with peg interferon alpha-2a monotherapy, and with telbivudine monotherapy in treatment naïve, HBeAg- positive CHB patients. Recruitment ongoing – 117/300 patient enrolled.
CLDT600A2407	Randomised, open-label, controlled, multicenter, exploratory trial to characterise the results of daily oral administration of telbivudine or entecavir given over 12 weeks on the kinetics of HBV DNA in adults with HBeAg- positive compensated chronic hepatitis B.

5.3 Summary of methodology of relevant RCTs

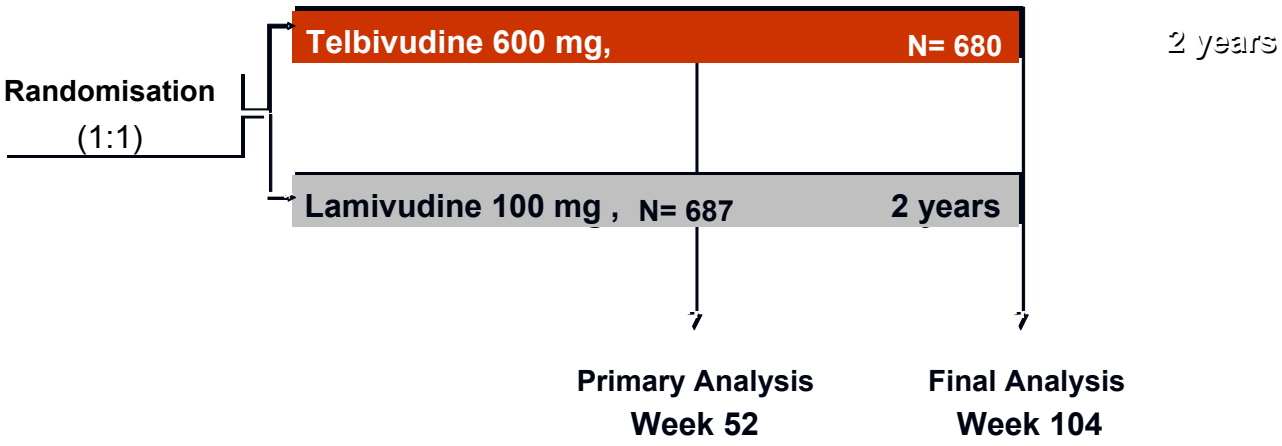
As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

The GLOBE trial was a randomised, double-blind, Phase III, registration trial comparing the clinical efficacy, safety and tolerability of telbivudine (600mg/day) versus lamivudine (100 mg/day) for 104 weeks [35]. Patients with CHB were recruited from 20 countries and had to be either nucleoside-naïve compensated HBeAg-positive or HBeAg-negative. In total, 1367 patients were recruited. Eligible patients were randomised (1:1) to receive telbivudine 600mg or lamivudine 100 mg, each with matching placebo, once daily as oral tablets (Figure 2).

Figure 2: Overview of GLOBE study design.



Treatment assignments were stratified by HBeAg status (positive or negative) and by serum ALT level (above or below 2.5 times the upper limit of normal). Within each stratum, patients were randomised using block sizes of four.

Blinding was performed using a double-blind, double-dummy procedure. Placebo tablets and capsules identical in appearance to telbivudine and lamivudine, respectively, were supplied in packaging to make them indistinguishable from the active drugs to the patients and the study personnel. To maintain blinding throughout the trial, and to facilitate study drug dispensation through the interactive voice response system (IVRS), capsules and tablets for each treatment group were packaged into uniquely numbered kits, each containing two bottles: one with active or placebo telbivudine tablets; and one with active or placebo lamivudine capsules. Patients were provided with a study drug kit after randomisation at the Baseline visit. One kit contained one month's supply of the study drug. Study drug was dispensed to patients on a schedule that would ensure uninterrupted dosing throughout the treatment interval. The kit number was entered into the source document and the CRF.

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Patients were required to meet the eligibility criteria as defined in the protocol. These criteria are summarised below:

Inclusion criteria:

- Male or female, 16-70 years of age.
- Documented chronic hepatitis B, defined by:
    - clinical history compatible with a diagnosis of chronic hepatitis B;
    - detectable serum HBsAg at the screening visit;
    - HBeAg-positive or HBeAg-negative at the screening visit;
    - elevated serum ALT level (1.3-10 x ULN) at the screening visit
    - liver biopsy within 12 months prior to randomisation, with histology compatible with chronic hepatitis B
- Screening serum HBV DNA level ≥6 $\log_{10}$ copies/mL.
- Patient willing and able to comply with the study drug regimen and all other study requirements.
- The patient or guardian provided written informed consent to participate in the study.

Exclusion criteria:

- Patient was pregnant or breastfeeding. Women of childbearing potential had a negative serum beta-human chorionic gonadotropin (β-HCG) at screening.
- Patient was of childbearing potential (men and women) and unwilling to use a barrier method of contraception.
- Patient was co-infected with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV-1 or HIV-2).
- Patient had previously received lamivudine or an investigational anti-HBV nucleoside or nucleotide analogue at any time.
- Patient had received interferon or other immunomodulatory treatment for HBV infection in the 12 months before screening for this study.
- Patient had a medical condition that required prolonged or frequent use of systemic acyclovir or famciclovir.
- Patient had a history of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or other clinical signs of hepatic decompensation.
- Patient had a history of HCC or findings suggestive of possible HCC.

- Patient was currently abusing alcohol or illicit drugs, or had a history of alcohol abuse or illicit substance abuse within the preceding 2 years.

- Patient had a medical condition that required frequent or prolonged use of systemic corticosteroids, or requiring the use of potentially hepatotoxic or nephrotoxic drugs.

- Patient had been on warfarin or other anticoagulants during the 30 days prior to Screening or if anticoagulant therapy was expected to be required during the present study.

- Patient had one or more additional known primary or secondary causes of liver disease other than hepatitis B and Gilbert's syndrome or Dubin-Johnson syndrome.

- Patient had any other concurrent medical condition likely to preclude compliance with the schedule of evaluations in the protocol or likely to confound the efficacy or safety observations of the study.

- Patient had a history of clinical pancreatitis.

- Patient was enrolled or planned to enroll in another clinical trial of an investigational agent while participating in this study.

- Patient had any of the following laboratory values at Screening:

    - Haemoglobin <11 g/dL for men or <10 g/dL for women;
    - Absolute neutrophil count (ANC) <1,500/mm^3;
    - Platelet count <75,000/mm^3;
    - Serum creatinine ≥1.5 mg/dL;
    - Serum amylase or lipase ≥1.5 x ULN;
    - Prothrombin time (PT) prolonged by more than 3 seconds, (based on the ULN of the reference value) despite vitamin K administration;
    - Serum albumin <3.3 g/dL;
    - Total bilirubin ≥2.0 mg/dL; and
    - Alpha-fetoprotein (AFP) >50 ng/mL

Patient Disposition

There were 1,367 patients included in the ITT analysis, of whom 921 were HBeAg-positive (458 in the telbivudine group and 463 in the lamivudine group) and 446 were HBeAg-negative patients (222 in the telbivudine group and 224 in the lamivudine group) [35]. There was no significant difference between patients randomised to telbivudine and those randomised to lamivudine with regard to baseline demographics. HBeAg-positive patients were approximately 10 years younger and had higher HBV DNA levels than HBeAg-negative patients, but this is consistent with the natural history of CHB. Table 3 shows the demographics by treatment and serostatus [35].

Figure 3: Baseline Demographics and Patient Characteristics, GLOBE (ITT population)

Parameter/ Statistic	HBeAg-positive		HBeAg-negative	
	Lamivudine N=463	Telbivudine N=458	Lamivudine N=224	Telbivudine N=222
Age in years (range)	33 (16-67)	32 (16-63)	43 (18-68)	43 (17-68)
Gender Male n (%)	351 (76)	333 (73)	178 (80)	174 (78)
Race (%)				
Caucasian	12	11	25	21
Asian (Chinese)	80 (57)	83 (58)	64 (46)	65 (52)
African/African American	2	1	1	1
Hispanic/Latino	1	<1	2	1
Middle Eastern/Indian	2	2	2	3
Other	4	3	6	9
HBV DNA, log_{10} copies/mL				
Mean (range)	9.5 (4-16)	9.5 (4-16)	7.4 (4-12)	7.7 (3-13)
Median	9.6	9.6	7.1	7.2
HBV serostatus n (%)				
HBeAg-positive	442 (95)	432 (95)	4 (2)	8 (4)
HBeAb-positive	63 (14)	61 (13)	220 (98)	215 (97)
HBsAg-positive	462 (100)	458 (100)	224 (100)	222 (100)
HBsAb-positive	21 (5)	17 (4)	8 (4)	7 (3)
Time since diagnosis, n (%)				
>1 year ago	363 (78.4)	365 (79.7)	195 (87.1)	206 (92.8)
>6 months to 1 year	65 (14.0)	53 (11.6)	22 (9.8)	11 (5.0)
≤6 months	35 (7.6)	40 (8.7)	7 (3.1)	4 (1.8)
Data missing	0	0	0	1 (0.5)
Duration[1], years mean (SD)	6.2 (6.24)	6.0 (6.54)	8.7 (7.46)	9.2 (7.96)

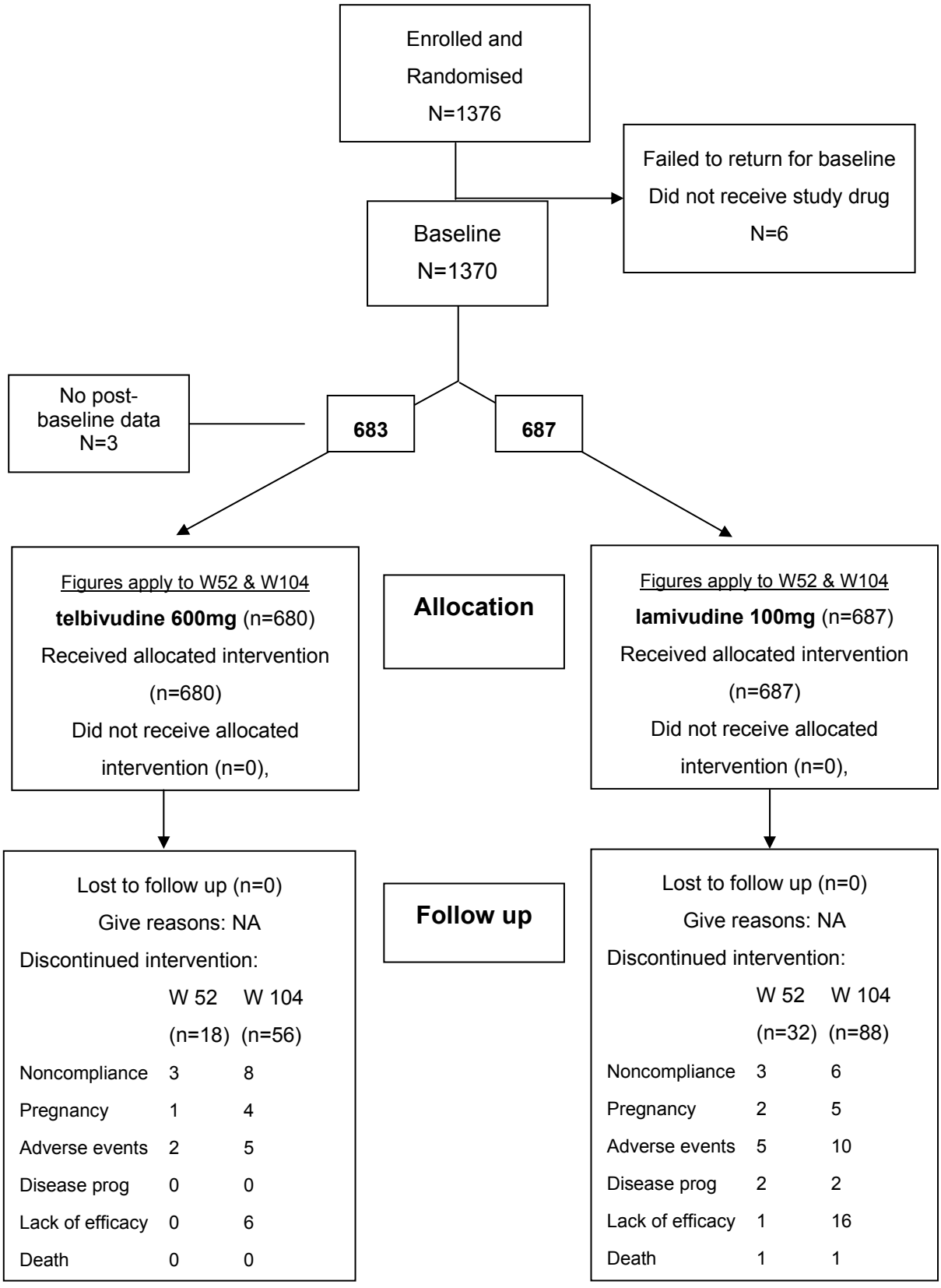
[1] Data missing from one lamivudine patient
Data from Lai et al., 2006°

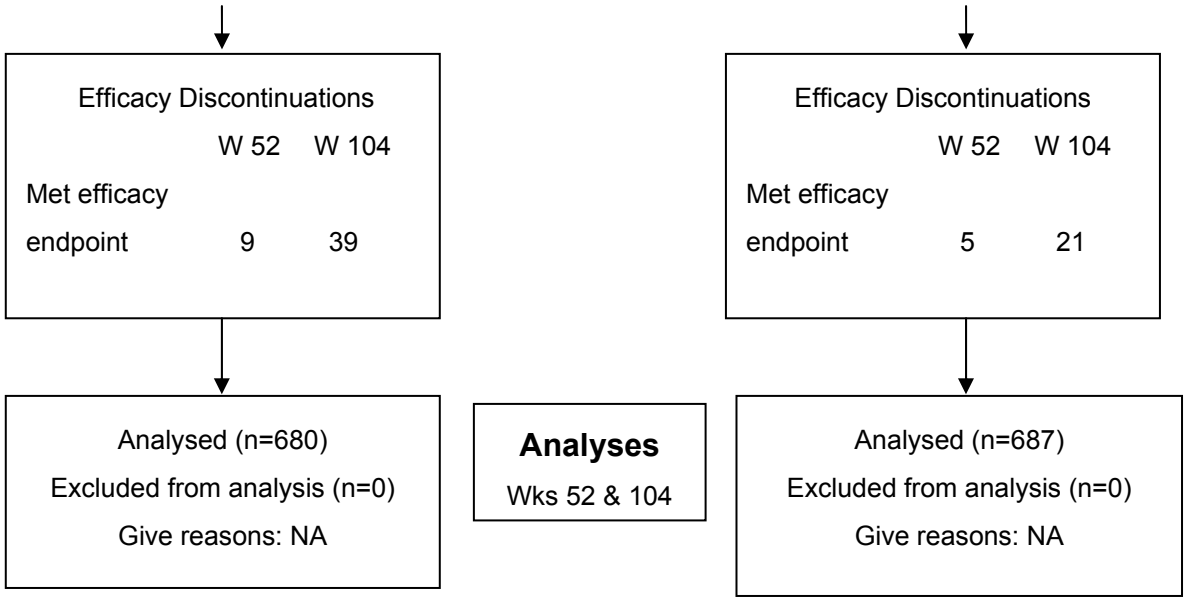
5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The CONSORT flow chart (Figure 4) for GLOBE is presented below.

Figure 4: Consort Flow Chart for GLOBE Study





5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Study 007 evaluated accepted outcomes used to demonstrate clinical efficacy of anti-HBV drugs. The efficacy measurements included HBV DNA , ALT, HBeAg, HBeAb, HBsAg, HBsAb, and liver histology. The measurements are those recommended by the regulatory authorities in their guidelines for the development of CHB treatments and are also those used in regulatory approval studies of other anti-HBV therapies. Further, these measures include recommended measures of efficacy in the current guidelines from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Asia-Pacific Association for the Study of the Liver (APASL); [33, 34, 36, 37].

EASL International Consensus Conference On Hepatitis B

Primary efficacy endpoint: Therapeutic Response

The primary efficacy endpoint for Study 007 measured at weeks 52 and 104 was a composite serologic endpoint "Therapeutic Response" defined as:

Suppression of HBV DNA <5 $\log_{10}$ copies/mL
Plus *Either*
Clearance of detectable HBeAg
Or
ALT normalisation (measure of liver function)

This composite Therapeutic Response endpoint incorporates the "Virologic Response" endpoint used in early interferon trials in HBeAg-positive patients [18, 38] and a composite efficacy endpoint comprising HBV DNA suppression and ALT normalisation which was used in several large clinical trials involving HBeAg-negative patients with chronic hepatitis B [39, 40]. Finally the components of the primary efficacy endpoint are aligned with the guideline-recommended clinical endpoints (AASLD and APASL guidelines).

Key secondary efficacy endpoint: antiviral efficacy

A key secondary antiviral efficacy endpoint measured at 52 and 104 weeks was HBV DNA level. In Study 007, HBV DNA assessments were conducted at screening, baseline and each post-baseline study visit up to 104 weeks. HBV DNA endpoints consisted of:

- ***HBV DNA suppression:*** the mean and median reduction in HBV DNA level from baseline, and for patients with ≥6 $\log_{10}$ copies/ml at baseline, the proportion of patients achieving a reduction in HBV DNA to <5 $\log_{10}$ copies/ml.

- ***HBV DNA PCR negativity*****:** the proportion of patients with undetectable HBV (below 300 copies/ml).

Other secondary efficacy endpoints

E antigen response (HBeAg seroconversion):
For HBeAg-positive patients only, secondary endpoints included the proportion of these patients experiencing a response in terms of loss of detectable eAg from serum (HBeAg loss), seroconversion (HBeAg loss plus gain of detectable anti-HBe antibody), and virologic response, which is HBeAg loss and reduction in HBV DNA to <5 $\log_{10}$ copies/ml.

Histologic response:
Changes in liver histology are considered important because they offer a true insight into the level of liver damage, regardless of other surrogate markers. Both the Knodell histology activity index (HAI) scoring method and the Ishak fibrosis scoring method were chosen to assess liver histology in this study. The fibrosis component score in the Knodell HAI scoring system is limited to four discontinuous integer scores (0, 1, 3, 4), corresponding to only four defined variations of fibrosis findings. Many hepatopathologists consider the Ishak fibrosis scoring method preferable, because seven different patterns of fibrosis-related changes are defined, allowing more precise evaluations, and the Ishak scoring system is a continuous integer scale (0-6), which is

more amenable to statistical analyses.
In Study 007, this outcome was measured at baseline and week 52 when liver biopsy samples were taken, and was defined as the proportion of patients achieving a ≥2 point reduction in Knodell necroinflammatory score without a worsening in Knodell fibrosis score. The Knodell necroinflammatory score is the sum of the first 3 components of the Knodell histology activity index, and scores can be 0-22 [41]. The fibrosis score is another component of the Knodell system measured on a 0-4 discontinuous scale. A separate assessment of fibrosis score was also made using the Ishak fibrosis score. Liver biopsies were not performed at week 104 owing to the invasive nature of the procedure.

Serum ALT changes:
Serum aminotransferase elevations in patients with HBV indicate enzyme release from inflamed liver and tend to precede structural changes detectable on biopsy histology. Hence, one of the endpoints included in Study 007 was ALT normalisation (the proportion of patients with elevated ALT levels at baseline (>ULN) who return to ALT within normal limits).

Treatment completion due to efficacy

The proportion of HBeAg-positive and HBeAg-negative patients who achieved specified antiviral efficacy at week 52, and were therefore deemed appropriate for treatment discontinuation, was assessed. For HBeAg-positive patients, efficacy was defined as achieving virologic response when treatment could be discontinued. For HBeAg-negative patients, this was defined as achieving HBsAg loss at week 52.

Virologic breakthrough and treatment emergent resistance

The 104 week CSR has been used for all results and definitions. The proportion of patients experiencing virologic breakthrough at week 48, 92 and 104 were evaluated according to pre-specified protocol definitions and also according to post hoc definitions which evolved during the second year of the study:

1. Protocol defined Virologic Breakthrough; An increase in HBV DNA to $\geq$ 5 $\log_{10}$ copies/ml on 2 consecutive occasions in patients who had previously achieved post baseline virologic response (i.e. 2 values < 5 $\log_{10}$ copies/ml)

2. "1 log above nadir" Virologic Breakthrough: defined as a confirmed HBV DNA increase of ≥1 $\log_{10}$ copies/ml above nadir HBV DNA (the lowest post baseline HBV DNA level achieved) in those patients with a confirmed treatment response (i.e. ≥1 log reduction in HBV DNA).

3. Treatment emergent resistance: defined as per NIH guidelines as virologic breakthrough with evidence of genotypic resistance associated mutations.

Adverse events were recorded at each visit and comprehensive safety assessments were conducted

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

Sample size

The overall study hypothesis for this global Phase III trial was that telbivudine treatment would provide superior clinical and virologic efficacy for patients with chronic hepatitis B (both HBeAg-positive and HBeAg-negative), while exhibiting a clinical safety profile similar to, or better than, that of lamivudine. Primary analysis was conducted after all patients completed 52 weeks, final analysis was performed at week 104.

The sample size calculations were based on accruing at least 1200 patients, with at least 600 HBeAg-positive patients and at least 400 HBeAg-negative patients.

Analyses were based on all randomised patients who received at least one dose of study medication. Histologic response analyses included all patients with evaluable pretreatment liver biopsies, similar to previous studies.

The GLOBE trial was intended to demonstrate effects in both HBeAg subpopulations or in the pooled population, if trends in both subpopulations warranted pooling. The primary endpoint was assessed using a three-step method. First, both HBeAg subpopulations were analysed separately utilising an alpha level of 0.0432 (95.68 percent confidence interval). If both subpopulations met non-inferiority criteria (confidence intervals for the treatment difference exclude –15 percent), treatments would be compared for superiority within each subpopulation.

If statistical significance was not established within both HBeAg subpopulations, a statistical test for interaction between the treatment group and HBeAg subpopulations was planned, with significance defined at the alpha level of 0.15. With no interaction, a statistical analysis for the overall patient population would be performed using an alpha level at 0.000933 to protect the overall alpha at 0.00125. Demonstration of non-inferiority was a precursor to superiority testing.

HBeAg subpopulations were not pooled because of this statistical interaction between treatment effect and HBeAg subpopulation. For secondary endpoints, treatment effects were to be compared, first for non-inferiority and then for superiority, according to a pre-specified hierarchy.
Treatment comparisons of categorical endpoints were assessed using a weighted Cochran-Mantel-Haenszel method, adjusting for randomisation strata. For continuous variables, analysis of variance was performed with each stratified group as a factor. Reported *P*-values are 2-sided and not adjusted for multiple testing.

Populations for analyses

Intent-to-treat (ITT) population for the efficacy evaluation

All randomised patients who presumptively received at least one dose of study medication with at least one observation after Baseline were to be included in the ITT analyses. Patients who received the wrong study medication were to be analysed according to the group to which they were randomised. Patients who had treatment discontinued for efficacy were to have post-treatment endpoint values summarised separately. The use of concomitant medications was to be tabulated using WHO drug classifications and summarised by treatment group.
Censoring- Any patient who received prohibited medications while on study was to be included in the ITT analyses, but the data were to be censored at the day they first took the prohibited medication. Prohibited medications were to include (but were not limited to):

- All investigational drugs other than telbivudine, investigational anti-HBV drugs such as adefovir, tenofovir, emtricitabine, lobucavir, entecavir, L-FMAU, L-Fd4C, or other nucleoside/nucleotide HBV drug candidates, various investigational interferons, or immunomodulators (e.g., IL-12, thymosin, etc.),
- All other treatments for hepatitis B, including lamivudine from other sources, alphainterferon, and commercially available treatments indicated for conditions other than chronic hepatitis B that are being investigated to treat or may have activity against HBV (e.g., ribavirin, ganciclovir, etc.),
- Prolonged use of systemic acyclovir or famciclovir, defined as episodic treatment with these agents for periods exceeding 10 days every 3 months, or chronic suppressive therapy.

Elevated ALT population

The “elevated ALT population” population was a pre-defined subset of the efficacy analysis populations, and includes all patients in the ITT population whose Screening ALT value was ≥ 2.0x ULN. This subpopulation was to be used to derive analyses of key efficacy parameters that will allow comparisons to historical results from interferon treatment studies, which typically required patients to have pretreatment ALT levels ≥ 2.0x ULN. Importantly, it corresponds to the patient population recommended for treatment under current AASLD and APASL guidelines, and is consistent with the EASL guidelines [33, 34, 37].

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any ‘commercial in confidence’ data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- How was allocation concealed?

The investigators and personnel involved in monitoring remained blinded throughout all periods of the study. Unblinding for individual patients was to occur only if the global medical monitor, sponsor medical monitor and the site investigator agreed that it was necessary for the safety of the patient. Emergency code breaks were to be performed by the global medical monitor or the sponsor medical monitor using the IVRS.

- What randomisation technique was used?

The IVRS was used to randomly assign patients to treatment groups. Randomisation was to occur in a 1:1 ratio across the 2 treatment groups (i.e., telbivudine 600 mg/day or lamivudine 100 mg/day), and was stratified according to patient HBeAg status and ALT level.

- Was a justification of the sample size provided?

The sample size calculations were based on accruing at least 1200 patients, with at least 600 HBeAg-positive patients and at least 400 HBeAg-negative patients. Calculations were based on historical response rates for patients treated with lamivudine, together with difference assumptions for telbivudine. For the Therapeutic Response endpoint, this sample size provided 99% power for the non-inferiority claim, with an assumption of a 15% non-inferiority criterion, and 92% power for the superiority claim if the response rate on telbivudine was 15% better than lamivudine. The study provided adequate power overall and for the subpopulations of HBeAg-positive and HBeAg-negative patients separately at one year for Therapeutic Response (the primary efficacy endpoint) and for Histologic Response (the key secondary efficacy endpoint). For the key secondary efficacy variable, Histologic Response at Week 52, the study had 84% and 94% power in the HBeAg-negative and HBeAg-positive subpopulations, respectively, and 92% power in the overall population for the non-inferiority claim. The detailed power calculations were based on an assumption of 7% and 10% dropout rates at 1 and 2 years, respectively, 20% missing histologic data, and a 50% Therapeutic Response rate in lamivudine recipients.

- Was follow-up adequate?

Follow up was adequate, reflected by the fact that 2 year data was available for the entire ITT population of 1367 patients and reasons for discontinuation were clearly documented at each stage (see Figure 4). On completion of the 2 year GLOBE study, patients were enrolled into an extension protocol for an additional 2 years of therapy (ongoing Study 022) to asses the long term efficacy and safety of telbivudine.

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

No, GLOBE was a double-blinded trial.

- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.

GLOBE was a parallel group design.

- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?

Patients were recruited at 112 centres in 20 countries: Australia; Canada; China; Czech Republic; France; Germany; Greece; Hong Kong; India; Italy; Korea; New Zealand; Poland; Singapore; Spain; Taiwan; Thailand; Turkey; United Kingdom and United States. Three of the centres were in the UK.

- How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.

Most patients were of Asian origin. This population is relevant to the UK as a high proportion of CHB cases occur in migrant communities within UK (Hep B Foundation Report, Nov 2007; NICE TA96).

It is important to note, however, that results from Caucasian patients were similar to Asian patients. Within the 2 racial/ethnic subgroups, in both HBeAg-positive (Table 3) and HBeAg-negative (Table 3) patients, telbivudine exhibited consistently better outcomes for Therapeutic Response, HBV DNA reduction and PCR-negative HBV DNA levels, lower rates of Virologic Breakthrough, and similar or better Histologic response when compared with lamivudine.

Table 3: Key efficacy results by treatment and race/ethnicity at Week 104– HBeAg-positive ITT population

	Lamivudine	**Telbivudine**	**P-value***
Endpointsδ	**n/N (%)**	**n/N (%)**	
Asians	**N=371**	**N=380**	
Theraputic Response	182/371 (49.1)	245/380 (64.5)	<0.0001
Histologic Response, Week 52#	199/349 (57.0)	246/364 (67.6)	0.0032
HBV DNA decrease, mean (SE) log10 copies/mL†	-4.39 (0.17)	-5.81 (0.16)	<0.0001
HBV DNA PCR negative	150/371 (40.5)	217/380 (57.1)	<0.0001
ALT normalisation	232/357 (65.0)	266/365 (72.9)	0.0220
“1 log above nadir” Virologic Breakthrough	169/371 (45.5)	106/380 (27.9)	<0.0001
HBeAg seroconversion (HBeAg+ only)	88/357 (24.7)	108/363 (29.7)	0.1265
Caucasians	**N=55**	**N=52**	
Theraputic Response	27/55 (49.6)	32/52 (62.1)	0.2265
Histologic Response, Week 52#	28/54 (51.6)	29/51 (56.2)	0.6430
HBV DNA decrease, mean (SE) log10 copies/mL†	-4.66 (0.43)	-5.13 (0.43)	0.4361
HBV DNA PCR negative	20/55 (36.4)	29/52 (55.4)	0.0453
ALT normalisation	28/54 (52.7)	28/49 (56.8)	0.6788
“1 log above nadir” Virologic Breakthrough	23/55 (41.1)	17/52 (33.1)	0.3824
HBeAg seroconversion (HBeAg+ only)	15/50 (29.8)	16/43 (37.5)	0.4170

Other	**N=37**	**N=26**	
Theraputic Response	14/37 (38.3)	13.26 (50.0)	0.3601
Histologic Response, Week 52#	17/30 (50.8)	9/24 (36.5)	0.3112
HBV DNA decrease, mean (SE) log10 copies/mL†	4.40 (0.61)	-5.92 (0.80)	0.1372
HBV DNA PCR negative	8/37 (23.3)	9/26 (34.9)	0.3315
ALT normalisation	15/35 (45.7)	12/26 (45.3)	0.9743
"1 log above nadir" Virologic Breakthrough	19/37 (51.1)	8/26 (30.3)	0.0925
HBeAg seroconversion (HBeAg+ only)	6/35 (15.8)	4/26 (17.2)	0.8793

Note: Percentages and P-values calculated using Mantel-Haenszel weighted estimates based on randomisation strata.

* P-value for treatment group difference controlling for randomisation strata: ANOVA for continuous variables, difference between proportions for categorical variables.

δ Unless otherwise specified, endpoints were analysed at Week 104.

Analyses based on HBeAg-positive mITT population.

† Least-square mean

Table 4: Key efficacy results by treatment and race/ethnicity at Week 104–HBeAg-negative ITT population

Endpointsδ	**Lamivudine n/N (%)**	**Telbivudine n/N (%)**	**P-value***
Asians	**N=144**	**N=145**	
Theraputic Response	103/144 (71.7)	118/145 (81.3)	0.0522
Histologic Response, Week 52#	97/141 (68.9)	97/137 (70.8)	0.7294
HBV DNA decrease, mean (SE) log10 copies/mL†	-4.35 (0.20)	-4.86 (0.19)	0.0617
HBV DNA PCR negative	92/144 (64.1)	124/145 (85.3)	<0.0001
ALT normalisation	98/131 (74.9)	110/133 (82.7)	0.1228
"1 log above nadir" Virologic Breakthrough	35/144 (24.0)	11/145 (7.7)	0.0001
Caucasians	**N=56**	**N=46**	
Theraputic Response	34/56 (60.6)	32/46 (69.3)	0.3593
Histologic Response, Week 52#	33/54 (61.2)	26/45 (58.5)	0.7803
HBV DNA decrease, mean (SE) log10 copies/mL†	-3.55 (0.31)	-5.05 (0.32)	0.0012
HBV DNA PCR negative	26/56 (45.8)	32/46 (68.9)	0.0167

ALT normalisation	35/53 (66.0)	29/41 (70.8)	0.6208
"1 log above nadir" Virologic Breakthrough	23/56 (41.4)	11/46 (24.7)	0.0715
Other	**N=24**	**N=31**	
Theraputic Response	11/24 (45.8)	22/31 (71.0)	0.0532
Histologic Response, Week 52#	14/23 (60.9)	18/30 (59.9)	0.9387
HBV DNA decrease, mean (SE) log10 copies/mL†	-4.48 (0.52)	-5.53 (0.39)	0.1137
HBV DNA PCR negative	9/24 (37.5)	26/31 (83.8)	0.0001
ALT normalisation	12/23 (52.0)	19/29 (65.5)	0.3255
"1 log above nadir" Virologic Breakthrough	10/24 (41.6)	5/31 (16.2)	0.0284

Note: Percentages and P-values calculated using Mantel-Haenszel weighted estimates based on randomisation strata.

* P-value for treatment group difference controlling for randomisation strata: ANOVA for continuous variables, difference between proportions for categorical variables.

δ Unless otherwise specified, endpoints were analysed at Week 104.

Analyses based on HBeAg-positive mITT population.

† Least-square mean

In common with several earlier trials of HBV therapies, Study 007 enrolled patients with liver enzyme abnormalities $\geq$ 1.3 – 10 x ULN for ALT. Since international treatment guidelines recommend that treatment be limited to patients with ALT > 2 x ULN, the study population included some patients who might not be considered "treatment-eligible". Patients with ALT > 2x ULN nonetheless represented 70% of the study population. Analysis of this >2 x ALT subgroup revealed heightened responses and enhanced efficacy compared to the overall ITT population; statistical superiority was achieved in all prospectively defined measures of antiviral and clinical efficacy, most notably superior e-seroconversion and histological response rates and reduced virologic breakthrough were observed in this subgroup.

In conclusion, the GLOBE study is relevant to the UK in terms of both the population and the outcomes.

- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

Patients received 600 mg of telbivudine or 100 mg of lamivudine daily for 104 weeks. These are the standard doses for both agents as recommended in respective SPCs.. No dose modifications were permitted in the study because of the double-blind, double-dummy design. Doses do not have to be adjusted for age, gender, race, disease severity or other demographic variables. The telbivudine SPC recommends dose reductions in patients with impaired renal function (creatinine clearance < 50 ml/min based on single dose PK modelling) but, due to the double blind design, this could not be accommodated within the study protocol. Therefore, patients with renal dysfunction (serum creatinine > 1.5 mg/dl) were not admitted to the study.

- Were the study groups comparable?

Yes, the demographics and background characteristics of the telbivudine and lamivudine groups were similar.

- Were the statistical analyses used appropriate?

Yes.

- Was an intention-to-treat analysis undertaken?

Yes. All efficacy analyses were completed on an intention-to-treat basis.

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

Patients could be enrolled on the basis of histological reading of baseline biopsy performed within 12 months of study start, therefore it is possible that histological progression of disease may have occurred in patients with a long interval before start of study treatment, thus confounding assessment of change from baseline at 1 and 2 year intervals.

Unexpected over-representation of HBeAg-positive patients in the final study population may have influenced the power of the study to show statistically significant differences in the HBeAg-negative subgroup. The numbers expected were 700 e-positive (minimum 600, maximum 800) and 500 e-negative (minimum 400 and maximum 600). Actual final numbers were 900 e-positive and 467 e-negative; this unexpected imbalance may have influenced the analysis especially for the e-negative group.

The primary composite endpoint consisted of suppression of viral load to < 5 $\log_{10}$ copies/ml with either eAg loss or ALT normalisation. Since the component eAg loss was not applicable to eAg negative group, this effectively restricted the ability of the eAg negative patients to meet the primary efficacy endpoint. This handicap together with the suboptimal numbers of eAg negative patients recruited may explain why the differences in efficacy were less-marked for Telbivudine over lamivudine in the HBeAg negative subpopulation.

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

GLOBE trial-study 007

Both HBeAg-positive and eAg-negative patients were enrolled in the GLOBE trial. In line with the cost-effectiveness analysis and the scope of this submission results for these two groups of CHB patients are presented separately.

HBeAg-positive patients

Therapeutic response:
In HBeAg-positive patients, telbivudine demonstrated statistical superiority over lamivudine for the primary endpoint of therapeutic response at week 52 (75.3% vs 67.0%; P<0.0047). The improved response rate for telbivudine was maintained through to week 104.

Table 5: HBeAg-positive therapeutic response at week 52 and 104

Response Parameter	**Week 52**		**Week 104**	
	Telbivudine 600 mg (n=458)	**Lamivudine 100 mg (n=463)**	**Telbivudine 600 mg (n=458)**	**Lamivudine 100 mg (n=463)**
Number achieving therapeutic response	345	310	290	223
Percentage	**75.3**	**67.0**	**63.3**	**48.2**
% absolute difference (for telbivudine v lamivudine)	+8.3		+15.1	
95% Confidence intervals	(2.4, 14.2)		(8.6, 21.6)	
P value*	0.0047		<0.0001	

Secondary outcomes:

Telbivudine provided more rapid viral suppression than lamivudine, achieving significantly greater mean reductions in viral load (Table 6).

Table 6: HBeAg-positive patients (n=921): Virological, Biochemical and Serological Endpoints at Week 52 and 104 (GLOBE)

Response Parameter	Week 52			Week 104		
	Telbivudine 600 mg (n=458)	**Lamivudine 100 mg (n=463)**	**p-value**	**Telbivudine 600 mg (n=458)**	**Lamivudine 100 mg (n=463)**	**p-value**
Mean HBV DNA Reduction from Baseline[1]: log_{10} copies/mL ± (SEM)	-6.45 (0.11)	-5.55 (0.11)	<0.0001	–5.74 (0.15)	–4.42 (0.15)	<0.0001
Proportion of patients with PCR-nondetectable HBV DNA[1] (%)	60.0	40.4	<0.0001	55.6	38.5	<0.0001
ALT Normalisation[1] (%)	**76.8**	**74.3**	**0.3776**	**69.5**	61.7	0.0135
HBeAg loss[1] (%)	25.7	23.3	0.4038	35.2	29.2	0.0556
HBeAg seroconversion [1] (%)	22.5	21.5	0.7263	29.6	24.7	0.0947
HBeAg seroconversion As per guidelines[2] (%)	**28.2**	24.3	0.2644	36.2	27.9	0.0268
Virologic breakthrough Per protocol[1] (%)	**3.4**	**10.4**	**<0.0001**	23.3	37.1	<0.0001
HBV resistance Per protocol [3](%)	3.0	8.2	0.0007	21.7	34.1	<0.0001
Virologic breakthrough > 1 log over nadir [1] (%)	**5.9**	**15.3**	**<0.0001**	28.6	45.5	<0.001
HBV resistance >1 log over nadir[4] (%)	5.0	11.0	0.0007	25.1	39.5	<0.0001

* Virologic breakthrough and resistance determined at week 48

Sources: [1] 104 wk CSR NV-02B-007,Table 11-54; [2] in patients with ALT $\geq$ 2 x ULN,104 wk CSR Table 14.2.1.26; [3] IDIX-07-206 Table 8.2.1.1; [4] IDIX-07-206 Table 8.1.1.1

Telbivudine suppressed the viral load by -5.7 logs at Week 104 compared with a -4.4 log reduction seen in the lamivudine group (P<0.0001). PCR negativity (undetectable HBV DNA) was achieved in 56% of telbivudine treated patients vs 39% in the lamivudine group (P<0.0001) at Week 104. In addition, ALT normalisation was achieved in 70% of patients in the telbivudine group vs 62% of patients in the lamivudine group (P=0.0135).

In HBeAg-positive patients, telbivudine showed proportional advantages for HBeAg loss and HBeAg seroconversion with results meeting predefined statistical criteria for non-inferiority compared with lamivudine through Week 104 (e.g. 30% vs 25%; P<0.05). Sustained HBeAg loss was 84% in the telbivudine group and 89% in the lamivudine group and sustained HBeAg seroconversion was 83% in the telbivudine group and 88% in the lamivudine group. The post-treatment durability of HBeAg response was therefore over 80% [42].

Viral breakthrough and genotypic resistance were significantly less common with telbivudine, compared with lamivudine at weeks 52 and 104. Cumulative rates of viral breakthrough in the telbivudine and lamivudine groups were 3.4% vs 10.4% respectively at year 1 and 23.3% vs 38.0% respectively at year 2 (p<0.0001 for both). Resistance (breakthrough defined according to protocol plus confirmed genotypic changes) occurred in 3.0% telbivudine recipients, versus 8.2% with lamivudine (*P*<0.0007) at year 1 and 21.7% vs 34.1% respectively at year 2 (p<0.0001). Consistent with previous

reports, M204I was the only signature mutation associated with telbivudine resistance. Lamivudine resistance was based on the signature mutations M204I or M204V (for further genotypic analysis details at week 52, please refer to the NEJM, in press). In normal clinical practice, genotyping is not usually conducted routinely and therapeutic management is often based solely on viral rebound.

Efficacy outcomes in patients with elevated ALT (≥2 x ULN)

Currently, patients with ALT elevated ≥2 x ULN are those recommended for treatment in the widely followed guidelines (AASLD, APASL and EASL). HBeAg-positive patients with baseline ALT ≥2 x ULN represented nearly 70% of the HBeAg-positive ITT patient population in Study 007. This sub-group is relevant because it represents the majority of HBeAg-positive patients selected for treatment in the UK.

In this sub-group, telbivudine was statistically superior to lamivudine at week 104 for all prospectively defined measures of antiviral and clinical efficacy. As would be expected in view of the underlying rationale for treatment eligibility in current guidelines, statistical superiority was achieved on some measures where no significant difference had been seen in the overall HBeAg-positive patient population. Most notably, in telbivudine treated patients, HBeAg seroconversion was more frequent at week 104 (36% versus 28%, p=0.0268) as was histologic response at week 52 (69% versus 61%, p=0.0281). Viral breakthrough was significantly reduced in this patient group treated with telbivudine versus lamivudine Table 7.

These data not only confirm the relevance of the analysis of the ITT population but also suggest that telbivudine, used according to internationally recognised treatment guidelines, would be expected to achieve both superior viral suppression and HBeAg antigen responses as compared to current treatments and thus is likely to prevent the long term outcomes of cirrhosis, liver failure and HCC more effectively in the treatment-eligible subgroup.

Table 7: Key efficacy outcomes in ITT/ mITT HBeAg-positive patients with ALT ≥2 x ULN (all at week 104 except histologic response at week 52)

	Telbivudine- numbers of patients/all patients (%)	Lamivudine- numbers of patients/all patients (%)	% difference (telbivudine v lamivudine)	P value*
Therapeutic response	212/320 (66.3)	163/317 (51.4)	14.9	0.0001
HBV DNA mean reduction (SE) and mean difference – log_{10} copies/ml**	-5.80 (0.18)	-4.75 (0.18)	-1.05	0.0001
HBV DNA PCR negative	194/320 (60.6)	130/317 (41.0)	19.6	<0.0001
Histologic response	213/308 (69.2)	183/301 (60.8)	8.4	0.0281
HBeAg seroconversion	109/301 (36.2)	85/305 (27.9)	8.3	0.0268
ALT normalisation	225/313 (71.9)	195/312 (62.5)	8.6	0.0118
Virologic breakthrough (>1 log above nadir')	86/320 (26.9)	136/317 (42.9)	-16.0	<0.0001

* Percentages and p values calculated using Mantel-Haenszel weighted estimates

** Least squares mean

HBeAg-negative patients

Therapeutic response:

In HBeAg-negative patients, telbivudine and lamivudine demonstrated similar efficacy at 52 weeks which conformed to the statistical definition of non-inferiority In year 2 Telbivudine demonstrated no loss of efficacy and achieved statistical superiority over lamivudine for the primary endpoint of therapeutic response at Week 104 (78% vs 66%; P=0.0069).

	Week 52		Week 104	
	Telbivudine 600 mg (n=222)	**Lamivudine 100 mg (n=224)**	**Telbivudine 600 mg (n=222)**	**Lamivudine 100 mg (n=224)**
Number achieving therapeutic response	166	173	172	148
Percentage	**74.8**	**77.2**	**77.5**	**66.1**
% Difference (for telbuvidine v lamivudine)	-2.4		11.4	
95% Confidence intervals	(-10.6, 5.7)		(2.9, 19.9)	
P value*	0.5433		0.0069	

Secondary outcomes:

Viral load was suppressed by -5.0 logs in the telbivudine group vs -4.2 logs in the lamivudine group (P=0.0002) at week 104.

PCR negativity (undetectable HBV DNA) was achieved in 82% of telbivudine recipients versus 57% of lamivudine recipients (P<0.0001) at week 104.

Viral breakthrough and genotypic resistance were significantly less common with telbivudine, compared with lamivudine at week 52 and 104. Cumulative rates of viral breakthrough in the telbivudine and lamivudine groups were 2.1% and 8.5% respectively at year 1 whilst 8.4% and 20.7% respectively at year 2 (p<0.005 for both). Resistance (breakthrough defined according to the protocol plus confirmed genotypic changes) occurred in 2.1% of HBeAg-negative telbivudine recipients, compared to 8.5% with lamivudine (*P*<0.001) at year 1 and 8.4% versus 20.2% respectively at year 2 (p=0.0008). Consistent with previous reports and as seen with the HBeAg-positive group, M204I was the only signature mutation associated with telbivudine resistance with lamivudine resistance based on the signature mutations M204I or M204V.

Table 8: HBeAg-negative patients (n=446): Virological, Biochemical and Serological Endpoints at Week 52 and 104 (GLOBE)

Response Parameter	Week 52			Week 104		
	Telbivudine 600 mg (n=222)	**Lamivudine 100 mg (n=224)**	p-value	**Telbivudine 600 mg (n=222)**	**Lamivudine 100 mg (n=224)**	p-value
Mean HBV DNA Reduction from Baseline[1] : log_{10} copies/mL (± SEM)	-5.22 (0.13)	-4.40 (0.13)	<0.0001	–5.00 (0.15)	–4.17 (0.16)	0.0002
Proportion of patients with PCR-nondetectable HBV DNA[1] (%)	87.8	71.4	<0.0001	82.0	56.7	<0.0001
ALT Normalisation[1](%)	72.9	77.8	0.2466	77.8	70.1	0.0725
Virologic breakthrough Per protocol [1] (%)	2.1	8.5	0.0052	8.4	19.7	0.0013
HBV resistance Per protocol [2] (%)	2.1	8.5	0.0052	8.4	20.2	0.0008
Virologic breakthrough > 1 log above nadir[1] (%)	2.3	12.5	<0.0001	12.2	30.4	<0.0001
HBV resistance >1 log above nadir [3] (%)	2.3	10.7	0.0002	10.8	25.9	<0.0001

* Virologic breakthrough and resistance determined at week 48

Sources: [1] 104 wk CSR NV-02B-007 Table 11-55; [2] IDIX-07-206 Table 8.2.1.2; [3] IDIX-07-206 Table 8.1.1.2

Histologic outcomes (52 weeks only), HbeAg-positive and HbeAg-negative

Table 9 shows the histological improvement and change in Ishak fibrosis score at Week 52, with greater improvements in the telbivudine group compared with the lamivudine group. Biopsy samples were only taken at one year and not thereafter. Therefore, the time from baseline to improvement or worsening in liver histology is only one year and is a relatively short period for assessment of histological response. The impact of antiviral therapy on liver pathology is not as immediate as it would be on viral load and thus 52 weeks may be too early for observation of clinically relevant changes in pathology. The study was not powered to detect differences in all histological parameters and p-values are only reported for improvement in Ishak Fibrosis Score

Table 9: HBeAg-positive and –negative patients: Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (GLOBE) [43]

	HBeAg-positive		HBeAg-negative	
	Telbivudine 600 mg (n=439)[1]	**Lamivudine 100 mg (n=433)[1]**	**Telbivudine 600 mg (n=212)[1]**	**Lamivudine 100 mg (n=218)[1]**
Histological Response[2]				
Improvement	284 (64.7%)	244 (56.3%)[§]	141 (66.6%)	144 (66.0%)
No Improvement	100 (23%)	125 (29%)	53 (25%)	56 (26%)
Ishak Fibrosis Score[3]				
Improvement	166 (37.8%)	189 (43.6%)*	100 (47.1%)	99 (45.4%)**
No Change	175 (40%)	143 (33%)	69 (33%)	90 (41%)
Worsening	43 (10%)	37 (9%)	25 (12%)	11 (5%)
Missing Week 52 Biopsy	55 (13%)	34 (15%)	18 (8%)	18 (8%)

Histological assessment was conducted at Week 52 only.
[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2.
[2] Histological Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score.
[3] For Ishak Fibrosis Score, improvement defined as a ≥ 1-point reduction in Ishak fibrosis score from Baseline to Week 52.
[§] p=0.01
** p=0.0774*
*** p=0.7209*

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 0 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.

- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate.
- Tabulate and/or graphically display the individual and combined results.

As described in section 5.1, there is only one study (GLOBE) that recruited a patient population which satisfied the criteria of the licensed indication (Lai *et al*. accepted for publication in NEJM). Consequently, it was not possible nor necessary to undertake a meta-analysis of studies to inform this appraisal in accordance with the decision problem.

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.
Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.
Give a full description of the methodology used and provide a justification for the approach.

Indirect Comparison with Entecavir

Both telbivudine and entecavir are potent nucleoside analogues for the treatment of CHB. The phase III studies conducted with both of these antivirals were done in comparison with lamivudine, the standard of care. No comparative trials have been conducted for telbivudine versus entecavir and so an indirect comparison was considered.

Listing of all randomised trials considered for inclusion

The head-to-head trials of lamivudine versus entecavir identified through the search are listed in Table 10 along with a comment regarding their suitability for inclusion in this submission.

Table 10: Head-to-head trials comparing lamivudine with entecavir

Design	Regimen	Population	Citation	Suitable for inclusion in this submission?
Double-blind, double dummy, randomised, controlled trial	0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-positive patients who had not previously received a NA	Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. NEJM 2006; 354(10): 1001-1010. Gish ,RG, Lok, AS, Chang T-T, et al . Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterol. 2007; 133: 1437-1444	Yes; Common comparator is lamivudine; Similar design and population to telbivudine vs lamivudine trial.
Double-blind, double dummy, randomised, controlled trial	0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-negative patients who had not previously received a NA	Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. NEJM 2006; 354(10): 1011-1020.	Yes; Common comparator is lamivudine; Similar design and population to telbivudine vs lamivudine trial.
Double-blind, double dummy, randomised, controlled trial	0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-positive patients who had not previously received a NA	Gish RG, Chang TT, De Man RA, et al. Entecavir results in substantial virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in HBeAg(+) chronic hepatitis B patients (study ETV-022). *Hepatology*. 2005;42(Suppl 1):267A. [Abstract 181]	No; This is an abstract of the 2 year results from the study reported by Chang et al above. Only 69% of entecavir and 46% of lamivudine patients remain in the analysis at 2 years, thus no meaningful comparison vs the telbivudine trial can be made.
Double-blind, randomised, controlled trial	0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-negative patients who had not previously received a NA	Shouval D, Akarca US, Hatzis G, et al. Continued virological and biochemical improvement through 96 weeks of entecavir treatment in HBeAg(-) chronic hepatitis B patients (study ETV-027). *J Hepatol*. 2006;44(Suppl 2):S21-S22. [Abstract 45]	No; This is an abstract of the 2 year results from the study reported by Lai et al above. Only 15% of entecavir and 22% of lamivudine patients remain in the analysis at 2 years, thus no meaningful comparison vs the telbivudine trial can be made.
Double-blind, randomised, controlled trial	0.01 mg or 0.1 mg or 0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-positive or negative patients	Lai CL, Rosmawati M, Lao J, van Vlierberghe H, Anderson FH, Thomas N et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. Gastroenterology 2002; 123(6):1831-1838.	No; Phase II dose-finding study with small numbers at the registered dose for 1st-line treatment and results pooled for HBeAg(+) & (-) patients.

Design	Regimen	Population	Citation	Suitable for inclusion in this submission?
Double-blind, randomised, controlled trial	0.01 mg or 0.1 mg or 0.5 mg entecavir once daily or 100 mg lamivudine once daily	HBeAg-positive or negative patients	Lai CL, Rosmawati M, Lao J, et al. A phase II study of Entecavir vs Lamivudine in adults with chronic hepatitis B.[abstract]. J Hepatol 2001; 34(1):24.	No; Abstract on the 24 week data from the phase II listed above.
NA	NA	NA	Lampertico P. Entecavir versus lamivudine for HBeAg positive and negative chronic hepatitis B. Journal of Hepatology 2006; . 45(3):457-460.	No; This paper is a 'Journal Club' type review of the paper by Lai et al 2006 listed above.
To assess HBV intrahepatic covalently closed circular DNA levels	As per Chang et al 2006 and Lai et al 2006	A subset of patients enrolled in the Chang et al 2006 and Lai et al 2006 trials	Wong DKH, Yuen M-F, Ngai VWS, Fung J, Lai C-L. One-year entecavir or lamivudine therapy results in reduction of hepatitis B virus intrahepatic covalently closed circular DNA levels. Antiviral Therapy 2006; 11(7):909-916.	No; The outcome of interest is not relevant to this submission. Patients are a subset from the 2 included trials above.

NA = nucleoside analogue

Assessment of the measures taken by investigators to minimise bias

NOTE: Most of the text in this and subsequent sections is copied directly from the Chang et al and Lai et al published papers.

For both studies a secure randomisation method was used and treatment administration and assessment was double-blinded.

Table 11: Summary of the measures undertaken to minimise bias in the RCTs in the indirect comparison

	Randomisation	Blinding	Follow-up
Chang et al 2006	Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each centre	Liver biopsies were evaluated by a central independent histopathologist who was blinded to the patient's treatment assignment, biopsy sequence and clinical outcome. Data were unblinded for statistical analysis after the database was locked.	Clinical management decisions were made at week 52 based on the 48 week serum results. Those who had a response (HBV DNA <0.7 MEq/mL and HBeAg loss) or did not have a response (HBV DNA >0.7 MEq/mL) discontinued treatment at week 52. Patients who had a response and discontinued were followed for a further 24 weeks. Those who had only a virological response (HBV DNA <0.7 MEq/mL and no HBeAg loss) were offered continued therapy for up to 96 weeks.
Lai et al 2006	Treatment assignments were allocated centrally on the basis of permuted block sizes of four that were assigned within each centre	Liver biopsies were evaluated by a central independent histopathologist who was blinded to the patient's treatment assignment, biopsy sequence and clinical outcome. Data were unblinded for statistical analysis after the database was locked.	Clinical management decisions were made at week 52 based on the 48 week serum results. Those who had a response (HBV DNA <0.7 MEq/mL and an ALT <1.25 xULN) or did not have a response (HBV DNA ≥0.7 MEq/mL) discontinued treatment at week 52. Those who had only a virological response (HBV DNA <0.7 MEq/mL and ALT at least 1.25 xULN) were offered continued therapy for up to 96 weeks.

Characteristics of the RCTs included in the indirect comparison

The design, interventions and outcomes of the telbivudine (GLOBE) trial have been detailed in Section 5.3. For entecavir, the Chang et al and Lai et al trials are outlined in Table 12. Following this the inclusion and exclusion criteria are listed in Table 13. These were essentially the same across the two studies. The demographics of the HBeAg-positive and HBeAg-negative patients included in the two trials are presented in Table 14.

The design of the telbivudine and the entecavir trials were similar, with the comparator arms being lamivudine 600 mg once per day, however the primary outcome was different and the primary analysis point for the telbivudine trial was at 52 weeks, whereas it was at 48 weeks for the entecavir trials. Both sets of trials evaluated HBeAg-positive and -negative patients separately. The minimum age at entry in all trials was 16 years and the other major inclusion/exclusion criteria were very similar.

The primary outcome in the telbivudine Study 007 was the composite outcome 'therapeutic response', defined for HBeAg-positive patients as: serum HBV DNA <5 $\log_{10}$ copies/mL and either HBeAg loss or ALT normalisation; and for HBeAg-negative patients as: serum HBV DNA <5 $\log_{10}$ copies/mL and ALT normalisation. However in the entecavir trials 'histologic response' was the primary outcome. This was a secondary outcome in the telbivudine trial. The other outcomes in common were 'HBV DNA undetectable (<300 copies/mL)', 'mean change in HBV DNA levels from baseline', and 'ALT normalisation'. The per protocol definition of ALT normalisation in the entecavir studies was a reduction from $\geq$ 1.3 x ULN to <1.25 x ULN and was therefore less stringent than for the Telbivudine study (007) where $\leq$1 x ULN was defined as the target for normalisation.

In terms of the demographics of patients included, the mean age of HBeAg-positive and –negative patients was 32 and 43 years, respectively in the telbivudine trial, and 35 and 44 years in the entecavir trials. The percentage of males was between 74 and 79% in all studies. The percentage of patients with Asian background was higher in the telbivudine trial at 82% of the HBeAg-positive cohort and 65% of the HBeAg-negative cohort, compared to approximately 57% and 40% respectively in the entecavir trials. The mean baseline HBV DNA levels were 9.5 and 7.5 $\log_{10}$ copies/mL in the telbivudine trial and approximately 9.6 and 7.6 $\log_{10}$ copies/mL in the entecavir trials. Fewer patients in the HBeAg-positive group of the telbivudine trial had previously received interferon therapy: 6% compared to 11% in the HBeAg-negative group; with approximately 13% of patients in each arm of the entecavir trials previously receiving interferon therapy.

Table 12: Comparative summary of characteristics of the RCTs included in the indirect comparison

Trial ID	Design & type of patients	Number of patients and centres	Interventions (drug dose, frequency, duration)	Primary outcome	Secondary outcome
Chang at el 2006	Double-blind, double-dummy, randomised, controlled trial. **HBeAg-positive** patients who had not received a nucleoside analogue within the last 24 weeks	715 randomised. Of those who received study drug and were analysed: entecavir n= 354 lamivudine n=355. 137 centres worldwide (including Australia)	0.5 mg entecavir once daily for 52 weeks, or 100 mg lamivudine once daily for 52 weeks.	Proportion of patients with histologic improvement, defined as a decrease by at least two points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score, at week 48, relative to baseline.	Reduction in HBV DNA level from baseline; proportion of patients with undetectable HBV DNA; decrease in Ishak fibrosis score; HBeAg loss or seroconversion; and normalisation of ALT.
Lai et al 2006	Double-blind, randomised, controlled trial. **HBeAg-negative** patients who had not received a nucleoside analogue within the last 24 weeks	1468 enrolled and screened 648 randomised. Of those who received study drug and were analysed: entecavir n= 325 lamivudine n=313. 146 centres worldwide (including Australia)	0.5 mg entecavir once daily or 100 mg lamivudine once daily	The proportion of patients with histologic improvement defined as improvement by at least two points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score at week 48, relative to baseline.	The reduction in the HBV DNA level from baseline and the proportion of patients with undetectable HBV DNA; the decrease in the Ishak fibrosis score; and normalisation of ALT.

Table 13: Eligibility criteria in the RCTs included in the indirect comparison

Trial ID	Inclusion criteria	Exclusion criteria
Chang et al 2006	• 16 years or older; • **HBeAg-positive** chronic hepatitis B and compensated liver function (total serum bilirubin ≤2.5mg/decilitre, prothombin time not >3secs longer than normal or an international normalised ratio not >1.5, serum albumin of at least 3.0g/decilitre, no history of variceal bleeding or hepatic encephalopathy); • detectable HBsAg for at least 24 weeks before screening; • evidence of CHB on baseline liver biopsy; • evidence of HBV DNA (at least 3 MEq per mL); and • ALT 1.3 to 10 times ULN	• co-infection with hepatitis C, hepatitis D, or HIV; • other forms of liver disease; • use of interferon alfa, thymosin α or an antiviral agent with activity against hepatitis B within 24 weeks before randomisation; • prior lamivudine therapy lasting more than 12 weeks; • alpha fetoprotein >100ng/mL; • history of ascites requiring diuretics or paracentesis; • previous treatment with entecavir.
Lai et al 2006	• 16 years or older; • **HBeAg-negative** chronic hepatitis B and compensated liver function (total serum bilirubin ≤2.5mg/decilitre, prothombin time not >3secs longer than normal or an international normalised ratio not >1.5, serum albumin of at least 3.0g/decilitre, no history of variceal bleeding or hepatic encephalopathy); • detectable HBsAg for at least 24 weeks before screening; • undetectable HBeAg • detectable anti-HBe • evidence of CHB on baseline liver biopsy; • evidence of HBV DNA (at least 0.7 MEq per mL); and • ALT 1.3 to 10 times ULN	• co-infection with hepatitis C, hepatitis D, or HIV; • other forms of liver disease; • use of interferon alfa, thymosin α or an antiviral agent with activity against hepatitis B within 24 weeks before randomisation; • prior lamivudine therapy lasting more than 12 weeks; • alpha fetoprotein >100ng/mL; • history of ascites requiring diuretics or paracentesis; • previous treatment with entecavir.

Table 14: Characteristics of participants in the RCTs included in the indirect comparison

	Chang et al 2006, HBeAg-positive			Lai et al 2006, HBeAg-negative		
	entecavir	**lamivudine**	**p-value**	**entecavir**	**lamivudine**	**p-value**
N randomised	354	355		325	313	
Age, mean ± SD (years)	35 ± 13	35 ± 13	1.00	44 ± 11	44 ± 11	1.00
Sex, male, n (%)	274 (77)	261 (74)	0.26	248 (76)	236 (75)	0.85
Race or ethnic group, n (%)						
Asian	204 (58)	202 (57)	0.91	122 (38)	129 (41)	0.74
White	140 (40)	141 (40)		193 (59)	176 (56)	
Black	8 (2)	8 (2)		8 (2)	7 (2)	
Other	2 (<1)	4 (1)		2 (<1)	1 (<1)	
Region, n (%)						
Asia or Australia	172 (49)	167 (47)	0.76	156 (48)	148 (47)	1.00
Europe	84 (24)	88 (25)		106 (33)	104 (33)	
Nth America	47 (13)	55 (15)		35 (11)	34 (11)	
Sth America	51 (14)	45 (13)		28 (9)	27 (9)	
Knodell necroinflammatory score	7.8 ± 2.98	7.1 ± 2.99	0.67	8.0 ± 2.7	7.7 ± 2.8	0.18
Ishak fibrosis score, mean ± SD	2.3 ± 1.27	2.3 ± 1.29	1.00	2.4 ± 1.2	2.5 ± 1.3	0.31
score ≥3 (bridging fibrosis), %	34	32	0.68	43	41	0.68
score ≥5 (cirrhosis), %	8	8	1.00	5	10	0.06
HBV DNA, log copies/mL, mean ± SD	9.62 ± 2.01	9.69 ± 1.99	0.64	7.6 ± 1.8	7.6 ± 1.7	1.00
ALT, IU/litre	140.5 ± 114.3	146.3 ± 132.3	0.53	141 ± 114.7	143 ± 119.4	0.83
Prior anti-HBV therapy, n (%)						
Interferon	46 (13)	46 (13)	1.00	42 (13)	39 (12)	0.91
Lamivudine	10 (3)	10 (3)	1.00	9 (3)	12 (4)	0.51

Source: Chang et al 2006, Tbl 1; Lai et al 2006, Tbl 1.

Outcome measures of the RCTs included in the indirect comparison

The primary and secondary outcome measures in the Chang et al and Lai et al trials are shown in Table 15. The primary outcomes were the same for patients who were HBeAg-positive [25] or -negative [44]. The secondary outcomes were also the same, except that HBeAg loss or seroconversion was not relevant for patients who were HBeAg-negative at baseline [44].

Table 15: Primary and secondary outcomes and statistical analyses of the RCTs included in the indirect comparison

Trial ID	Definition of outcome	Statistical analyses
Primary outcomes: Chang et al 2006: **HBeAg(+)** & Lai et al 2006 : **HBeAg(-)**	• Proportion of patients with histologic improvement on biopsy, defined as a decrease by at least two points in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score, at week 48, relative to baseline.	• The sample size had 90% power to demonstrate non-inferiority, assuming: response rates of 60% for 64% for entecavir and 60% for lamivudine, a 25% rate of missing biopsies at week 48, and a minus 10% boundary for the 95% lower CI for the difference in proportions. • First non-inferiority of entecavir compared to lamivudine was tested; if this was established then a test for superiority was performed. • Patients who could be evaluated had adequate baseline biopsy specimens with a Knodell necroinflammatory score of at least 2. • Patients with missing or inadequate biopsy specimens obtained at week 48 were considered not to have a histological response. • In proportion analyses of HBV DNA values, HBV serological data, and ALT levels, treated patients with a missing value for that endpoint were considered not to have a response for that endpoint. • T-tests based on linear regression models were used to compare means of continuous variables, adjusted for baseline measurements. • P-values are two-sided and were not adjusted for multiple testing.
Secondary outcomes: Chang et al 2006 : **HBeAg(+)**	• Reduction in HBV DNA level from baseline; • Proportion of patients with undetectable HBV DNA; • Decrease in Ishak fibrosis score; • HBeAg loss; • HBeAg seroconversion (HBeAg loss & the appearance of HBe antibody); • Normalisation of ALT Original defn: <1.25 xULN Amended defn: < ULN	
Secondary outcomes: Lai et al 2006 : **HBeAg(-)**	• Reduction in HBV DNA level from baseline; • Proportion of patients with undetectable HBV DNA; • Decrease in Ishak fibrosis score; • Normalisation of ALT < ULN	

The definitions for HBV resistance and the method of analysing the adverse event data in the entecavir trails are shown in Table 16.

Table 16: Methods used to determine HBV resistance and safety in the RCTs included in the indirect comparison

HBV resistance	
Chang et al, HBeAg(+)	An extensive resistance analysis was undertaken to identify emerging HBV polymerase substitutions that may be associated with reduced susceptibility to entecavir. All 339 available paired samples from patients in the entecavir group were submitted for genotypic analysis. HBV DNA was extracted and amplified by polymerase chain reaction (PCR), and amino acids 1 through 344 of the reverse transcriptase were sequenced as described elsewhere. Substitutions that emerged during therapy were inserted into recombinant clones and analysed in cell-culture phenotypic assays for any effect on susceptibility to entecavir. Within the lamivudine group, genotypic and phenotypic analyses were performed only on samples from patients meeting the criterion for virologic rebound (defined as a confirmed increase in HBV DNA by at least 1 log copy per milliliter from the nadir value, according to a PCR assay, during the administration of study medication).
Lai et al, HBeAg(-)	Two sampling schemes were used to identify emerging HBV polymerase substitutions that maybe associated with reduced susceptibility to entecavir. Paired samples from 211 randomly selected patients in the entecavir group were genotypically analysed. HBV DNA was extracted and amplified with the use of PCR, and amino acids 1 through344 of the reverse transcriptase were sequenced as described elsewhere. Substitutions that emerged during therapy were inserted into recombinant clones and analysed in cell-culture phenotypic assays for susceptibility to entecavir. The second sampling scheme involved genotypic and phenotypic analyses of all paired samples from all patients meeting the criterion for virologic rebound (defined as a confirmed increase in the HBV DNA level by at least 1 log [on a base-10 scale] copy per milliliter from the nadir value, according to PCR assay, while the patient was receiving the study medication).
Safety analysis	
Chang et al, HBeAg(+)	The safety analysis included data from all 709 treated patients during treatment, including the second year of treatment for patients who continued for more than 52 weeks. The primary safety end point was the proportion of patients who discontinued the study medication because of clinical or laboratory-determined adverse events. Other safety evaluations included analyses of adverse events, serious adverse events, and deaths. Hepatitis flares during treatment were defined as elevations in the ALT level to more than twice the baseline level and to more than 10 times the upper limit of normal. Post-treatment flares were defined as elevations in ALT to more than twice the reference level and to more than 10 times the upper limit of normal, where the reference level was the lesser of the baseline value and end-of-treatment value.
Lai et al, HBeAg(-)	The safety analysis included data from all 638 treated patients during treatment, including the second year of treatment for patients who continued for more than 52 weeks. The primary safety end point was the proportion of patients who discontinued the study medication because of clinical or laboratory-determined adverse events. Other safety evaluations included analyses of adverse events, serious adverse events, and deaths. Flares of hepatitis during treatment were defined as elevations in the alanine aminotransferase level to more than twice the baseline level and to more than 10 times the upper limit of normal. Post treatment flares were defined as elevations in alanine aminotransferase to more than twice the reference level and to more than 10 times the upper limit of normal, where the reference level was the lesser of the baseline value and the end-of treatment value.

Efficacy results: Entecavir

Histology outcome

Histology is regarded as a longer-term outcome and, for meaningful comparisons, needs to be monitored over years rather than months.
The proportion of patients with histological improvement at week 48 in each of the 2 key trials for entecavir and for telbivudine Study 007 is shown in
Table 17. Entecavir and telbivudine were significantly more effective than lamivudine in terms of the proportion of responders in both trials.

Table 17 Primary outcome in the RCTs included in the indirect comparison

	entecavir	lamivudine	diff (95% CI)	p-value
Chang et al, HBeAg-positive pts	**N=314**	**N=314**		
Histological improvement n (%)	226 (72)	195 (62)	9.9 (2.6, 17.2)	0.009
Lai et al, HBeAg-negative pts	**N=296**	**N=287**		
Histological improvement n (%)	208 (70)	174 (61)	9.6 (2.0, 17.3)	0.01

Source: Chang et al 2006, Tbl 2; Lai et al 2006, Tbl 2.

Secondary outcomes

The secondary outcomes reported for HBeAg-positive and HBeAg-negative patients are shown in

Table **18**.

Table 18 Secondary outcomes in the RCTs included in the indirect comparison

	entecavir	lamivudine	diff (95% CI)	p-value
HBeAg-positive pts	**N=354**	**N=355**		
HBV DNA <300 copies/mL,[a] n(%)	236 (67)	129 (36)	30.3 (23.3, 37.3)	<0.001
Mean change in HBV DNA from baseline, log copies/mL,[a] m±SD	-6.9 ± 2.0	-5.4 ± 2.6	-1.52 (-1.78,-1.27)	<0.001
ALT normalisation (≤1xULN), n(%)	242 (68)	213 (60)	8.4 (1.3, 15.4)	0.02
Loss of HbeAg, n(%)	78 (22)	70 (20)	2.3 (-3.7, 8.3)	0.45
HBeAg seroconversion, n(%)	74 (21)	64 (18)	2.9 (-2.9, 8.7)	0.33

	entecavir	lamivudine	diff (95% CI)	p-value
HBsAg loss, n(%)	6 (2)	4 (1)	0.6 (-1.2, 2.3)	0.52
HBeAg-negative pts	**N=325**	**N=313**		
HBV DNA <300 copies/mL,[a] n(%)	293 (90)	225 (72)	18.3 (12.3, 24.2)	<0.001
Mean change in HBV DNA from baseline, log copies/mL,[a] m±SD	-5.0 ± 1.7	-4.5 ± 1.9	-0.43 (-0.6, -0.3)	<0.001
ALT normalisation (≤1xULN), n(%)	253 (78)	222 (71)	6.9 (0.2, 13.7)	0.045

Source: Chang et al 2006 [25], Tbl 3; Lai et al 2006 [44], Tbl 3.
[a] Measured by PCR

In both HBeAg-positive and HBeAg-negative patient populations entecavir was superior to lamivudine for reduction in viral load and the proportion of patients with undetectable HBV DNA. The importance and relevance of reduction in HBV DNA as an accurate predictor of long term outcomes, and as an influencer of long term clinical benefits has already been described in the answer to question 5b. It is interesting to note that, even though histological improvement was the primary endpoint in the entecavir studies, treatment responders were defined by HBV DNA reduction.

Entecavir was significantly better than lamivudine for the proportion of patients with ALT normalisation (however, the difference for the HBeAg-negative patients was borderline). Whilst ALT normalisation is useful as a marker of disease progression, levels may fluctuate for various reasons. In addition, liver damage and increased risk of cirrhosis may occur at levels within the normal range (<1 x ULN). Therefore, ALT levels must always be viewed within the context of the individual patient.

Entecavir and lamivudine were similar in terms of HBeAg loss and HBeAg seroconversion in the HBeAg-positive patients.

Efficacy results: Indirect Comparison

The results are presented below (Table 19).

Table 19: Summary of entecavir results at 48 weeks and telbivudine at 52 weeks

	Entecavir*	Lamivudine	Telbivudine#	Lamivudine
HBeAg positive patients	n=354	N=355	n=458	n=463
Viral suppression (log10 copies/ml)	-6.9	-5.4	-6.45	-5.55
Proportion of patients non-detectable by PCR (%)	67	36	60	40
ALT normalisation (%)	68	60	77	74
Histological improvement (%)	72	62	71**	61
e-seroconversion (%)	21	18	23	22
HBeAg negative patients	n=325	N=323	n=222	n=224
Viral suppression (log10 copies/ml)	-5.04	-4.53	-5.22	-4.40
Proportion of patients non-detectable by PCR (%)	90	72	88	71
ALT normalisation (%)	78	71	73	78
Histological improvement (%)	70	61	71**	70

**Chang et al. 2006, Lai et al. 2006,*
#Study 007 CSR,
***Telbivudine SPC June 2007*

A quantitative comparison of the data across the entecavir and telbivudine trials is difficult to perform, however a descriptive comparison emphasises the similarities between telbivudine and entecavir with respect to a number of important endpoints in the management of CHB. It can be seen from the above table that, regardless of the outcome measure, telbivudine appears to perform as well as entecavir. Thus, for viral suppression, PCR-negativity, ALT normalisation, histological improvement and e-seroconversion, telbivudine is superior to lamivudine and therefore a cost-effective first-line option.

It is impossible to compare, even indirectly, the resistance rates of telbivudine and entecavir at 2 years, because the data reported for entecavir at 2 years is not based upon the ITT population; only a subset of patients who commenced the study (69% of HBeAg-positive and 15% of HBeAg-negative patients) were allowed to continue therapy beyond 52 weeks and were followed-up to 2 years. The authors of the 2 year Entecavir paper [27] have summarised the limitations of their study design in the discussion section as follows:

> *The study was designed to evaluate the possibility of discontinuing treatment after meeting prespecified patient management criteria at week 52; therefore, the protocol specified that responders and nonresponders should discontinue treatment at or after week 52. As a result, another challenge when interpreting the second-year results derives from the absence of a cross-sectional presentation of response rates at week 96.* ***After week 52, it is not possible to provide an assessment in which all patients who originally started treatment are accounted for at a single time point under uniform treatment conditions. Therefore, the results from this study cannot be compared directly with other studies that evaluate continuous treatment in all patients through 2 years****, regardless of clinical course....*

Statistical indirect comparison of telbivudine and entecavir

As stated in section 3.5, because there was only one study (GLOBE – a comparison of telbivudine with lamivudine in HBeAg-positive and HBeAg-negative patients) it was not possible to undertake meta-analysis to inform this appraisal in accordance with the decision problem. The possibility of an indirect comparison was considered since data comparing entecavir with lamivudine are available. However a literature search revealed only one published study in HBeAg-positive patients [25] and one study in HBeAg-negative patients [44]. Therefore it was not possible to undertake a meta-analysis for entecavir. In the absence of meta-analyses for either comparator, a formal indirect comparison should not be considered valid [45].
While the patient selection criteria for the entecavir and telbivudine studies were broadly similar, there were substantial differences in the racial composition of the treatment groups in the various studies. As noted previously the proportions of white and asian patients differ between trials (Table 7 and Figure 3). In addition there are notable differences in terms of the HBV genotypes represented in the GLOBE and entecavir studies. Although the relevance of these differences to outcomes is unclear at this time, these observations highlight the potential pitfalls of between trial comparisons.

Comparison of Genotype distribution in Telbivudine (GLOBE) and entecavir studies (BEHOLD)

	A	B	C	D	Other
e-Ag +ve					
Globe (%)	6	26	57	11	1-2
Behold (%)	28	20	28	12	10
e-Ag-ve					
Globe (%)	6	26	39	27	1-2
Behold (%)	10	17	17	46	10

Although “naïve” indirect comparisons should be interpreted with caution, the lack of data mean that this is the only approach that can be undertaken. Thus, an indirect comparison in order to estimate the relative efficacies of telbivudine and entecavir. In all cases the 95% credible interval for the log relative risk between entecavir and telbivudine contained 0 or the 95% relative risk between entecavir and telbivudine contained unity. As such there is no statistical evidence that entecavir is significantly different from telbivudine, despite its higher acquisition cost. Further details are provided in Appendix A.

Safety results: Entecavir

The safety results from the 2 key trials comparing entecavir with lamivudine are shown in Table 20. Safety results for the key trial (Study 007) comparing telbivudine with lamivudine are presented in Section 4 (comparative safety).

In the HBeAg-positive patients, the most frequent adverse events (AEs) were headache,

upper respiratory tract infection, nasopharyngitis, cough, pyrexia, upper abdominal pain, fatigue and diarrhoea – most of which were of mild to moderate severity. Significantly more patients in the lamivudine group had ALT flares (particularly post-treatment) and more patients discontinued due to an AE: 9 in the lamivudine group (4 due to an increase in ALT) compared to 1 in the entecavir group (due to an increase in ALT). During treatment with lamivudine 2 deaths occurred, but neither was judged to be related to the study drug.

In the HBeAg-negative patients, the most frequent AEs were headache, upper respiratory tract infection, upper abdominal pain, influenza, nasopharyngitis, dyspepsia, fatigue, back pain, arthralgia, diarrhoea, insomnia, cough, nausea, and myalgia – most of which were of mild to moderate severity. In the entecavir group there were fewer discontinuations due to AEs compared to the lamivudine group (6 and 9 respectively) and none were due to ALT flares. In the post-treatment phase significantly more patients who had been treated with lamivudine experienced ALT flares. During treatment with entecavir 2 deaths occurred, but neither was judged to be related to the study drug.

Table 20: Safety data from the RCTs included in the indirect comparison

	entecavir	lamivudine	p-value
Chang et al, HBeAg-positive pts	**N=354**	**N=355**	
During treatment			
Any adverse event	306 (86)	297 (84)	0.34
Serious adverse event	27 (8)	30 (8)	0.78
Discontinuation due to adverse event	1 (<1)	9 (3)	0.02
ALT >2 x baseline & >10 x ULN	12 (3)	23 (6)	0.08
ALT >2 x baseline & >5 x ULN	37 (10)	59 (17)	0.02
Death	0	2 (<1)	0.50
Post-treatment follow-up	*N=134*	*N=129*	
ALT >2 x reference value & >10 x ULN	2 (1)	9 (7)	0.03
ALT >2 x reference value & >5 x ULN	3 (2)	16 (12)	0.002
Lai et al, HBeAg-negative pts	**N=325**	**N=313**	
During treatment			
Any adverse event	246 (76)	248 (79)	0.30
Serious adverse event	21 (6)	24 (8)	0.64
Discontinuation due to adverse event	6 (2)	9 (3)	0.44
ALT >2 x baseline & >10 x ULN	3 (<1)	5 (2)	0.50
ALT >2 x baseline & >5 x ULN	6 (2)	10 (3)	0.32
Death	2 (<1)	0	0.50
Post-treatment follow-up	*N=297*	*N=263*	
ALT >2 x reference value & >10 x ULN	23 (8)	29 (11)	0.19

	entecavir	lamivudine	p-value
ALT >2 x reference value & >5 x ULN	36 (12)	77 (29)	0.001

Source: Chang et al 2006 [25], Tbl 4; Lai et al 2006 [44], Tbl 4.

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.
If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.
Approximately 3614 subjects have been treated with telbivudine in clinical studies at a dose of 600 mg once daily (PSUR 2, Oct 2007) [46]. Assessment of adverse reactions is primarily based on the pivotal 007 GLOBE study in which 1,367 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=680 patients) or lamivudine (n=687 patients) for up to 104 weeks. The median duration of study drug treatment for the overall ITT population was the same for the two treatment groups (104.1 weeks).. The safety profiles of telbivudine and lamivudine were generally comparable in this study.

Clinical Adverse Events in the GLOBE Study

In clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity and not attributed to telbivudine. In the 007 GLOBE study patient discontinuations for adverse events, clinical disease progression or lack of efficacy were 0.6% for telbivudine and 2.0% for lamivudine.

Selected treatment-emergent, clinical adverse events graded moderate-to-severe, without consideration of study drug causality, during the pivotal 007 GLOBE study clinical trial, are presented in Table 21.

Table 21: Selected Treatment-Emergent Clinical Adverse Events[a] (Grade 2-4) of Moderate to Severe Intensity Reported in the 007 GLOBE Study

Body System/Adverse Event	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
All subjects with any Grade 2-4 AE	22%	22%
General		
Fatigue/Malaise[b]	1%	1%
Pyrexia	1%	<1%
Musculoskeletal & Connective Tissue		
Arthralgia	<1%	1.0%
Muscle-Related Symptoms[c]	2%	2%
Gastrointestinal		
Abdominal Pain[d]	<1%	<1%
Diarrhea/Loose Stools[e]	<1%	<1%
Gastritis	<1%	0
Respiratory, Thoracic, & Mediastinal		
Cough[f]	<1%	<1%
Nervous System		
Headache[g]	1%	2%

[a.] *Includes adverse events categorised as possibly/reasonably or not possibly/reasonably related to the treatment regimen by the Investigator. Excludes upper respiratory infection, pharyngitis/nasopharyngitis, post-procedural pain, influenza and influenza-like symptoms and laboratory abnormalities that were considered adverse events. Also excludes adverse events with a frequency of less than 0.7% in the LdT arm.*

[b.] *Includes preferred terms: fatigue and malaise*

[c.] *Includes preferred terms: back pain, fibromyalgia, muscle cramp, musculoskeletal chest pain, myalgia, myopathy, pain, pain in extremity, and tenderness.*

[d.] *Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain. Adverse events under preferred term "abdominal pain upper" with an event or lower level term descriptions of right upper quadrant pain were excluded from the abdominal pain category and coded under hepatic pain/RUQ pain.*

[e.] *Includes preferred terms: diarrhea, loose stools, and frequent bowel movements*

[f.] *Includes preferred terms: cough and productive cough*

[g.] *Includes preferred terms: headache, migraine, sinus headache, and tension headache*

Frequencies of selected treatment-emergent laboratory abnormalities in the GLOBE study are listed in Table 22.

Table 22: Selected Treatment-Emergent Grade 3-4 Laboratory Abnormalities[1] in Patients with Chronic Hepatitis B in the 007 GLOBE Study

Test	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
Creatine Kinase (CK) ≥ 7.0 x ULN	9%	3%
ALT >10.0 x ULN and 2.0 x baseline[2]	3%	5%
ALT (SGPT) >3.0 x baseline	4%	8%
AST (SGOT) >3.0 x baseline	3%	6%
Lipase >2.5 x ULN	2%	4%
Amylase >3.0 x ULN	<1%	<1%
Total Bilirubin >5.0 x ULN	<1%	<1%
Neutropenia (ANC ≤749/mm^3)	2%	2%
Thrombocytopenia (Platelets ≤49,999/mm^3)	<1%	<1%

[1] *On-treatment value worsened from baseline to Grade 3 or Grade 4 during therapy.*

[2] *American Association for the Study of Liver Diseases (AASLD) definition of acute hepatitis flare.*

Creatine kinase (CK) elevations were more frequent among subjects on telbivudine treatment, as shown above in Table 22 CK elevations occurred in both treatment arms; however median CK levels were higher in telbivudine-treated patients by Week 52. Grade 1-4 CK elevations occurred in 72% of telbivudine-treated patients and 42% of lamivudine-treated patients, whereas Grade 3/4 CK elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Most CK elevations were asymptomatic but the mean recovery time was longer for subjects on telbivudine than subjects on lamivudine. While there was not a uniform pattern with regard to the type of adverse event and timing with respect to the CK elevation, 8% of telbivudine-treated patients with Grade 1-4 CK elevations experienced a CK-related adverse event[1] (within a 30-day window) compared to 6% of lamivudine-treated patients. In this subgroup of patients with CK-related adverse events, 9% of telbivudine-treated patients subsequently interrupted or discontinued study drug. These patients recovered after study drug discontinuation or interruption. Less than 1% of telbivudine-subjects overall (n=3/680) were diagnosed with myopathy; these patients also recovered after study drug discontinuation.

As shown in Table 22, on-treatment ALT elevations were more frequent with lamivudine. Additionally, the overall incidence of on-treatment ALT flares, using AASLD criteria (ALT >10 x ULN and >2.0 x baseline), was slightly higher in the lamivudine arm (5.1%) than the telbivudine arm (3.2%). The incidence of ALT flares was similar in the two treatment

[1] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.

arms in the first six months. ALT flares occurred less frequently in both arms after Week 24, with a lower incidence in the telbivudine arm (0.4%) compared with the lamivudine arm (2.2%). For both lamivudine and telbivudine subjects, the occurrence of ALT flares was more common in HBeAg-positive subjects than in HBeAg-negative subjects. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis after Discontinuation of Treatment

There are insufficient data on post-treatment exacerbations of hepatitis after discontinuation of telbivudine treatment.

Adverse Events Listed in the SmPC

Table 23 lists the adverse reactions recorded in the first 52 weeks of treatment in the 007 GLOBE study by system organ class and by frequency using the following convention: common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Most reported adverse reactions were classified as mild or moderate in severity.

Table 23: Clinical adverse reactions in patients with chronic hepatitis B, treated with telbivudine 600 mg, reported by week 52 in the 007 GLOBE study*

Nervous system disorders	
Common	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	Blood amylase increased, diarrhoea, blood lipase increased, nausea, abdominal pain
Skin and subcutaneous tissue disorders	
Common	Rash
Musuloskeletal and connective tissue disorders	
Common	Blood creatine phosphokinase increased
Uncommon	Arthralgia, myalgia, myopathy
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Malaise
Hepatobiliary disorders	
Common	Blood alanine aminotransferase increased

* *Due to the sample size in the GLOBE trial there are insufficient numbers of patients to detect rare and very rare events.*

Grade 3/4 creatine kinase elevations (> 7 x ULN) occurred in 7.5% of telbivudine-treated patients and 3.1% of lamivudine-treated patients by week 52. Most creatine kinase elevations were asymptomatic and creatine kinase values typically decreased by the next visit on continued treatment. In the pivotal GLOBE study, higher pre-treatment CK values and Caucasian race were identified in both treatment groups as predictive factors for Grade 3/4 elevations during the first year of treatment.

Overall, the incidence of Grade 3/4 ALT flares from baseline to week 52 was 2.6% of telbivudine-treated and 4.6% of lamivudine-treated patients. The incidence of alanine aminotransferase (ALT) flares in the two treatment arms is further described in Table 24 (from baseline to week 24) and Table 25 (from week 24 to week 52) below.

Table 24: Analysis of categories of on-treatment ALT flares to week 24[2]

	HBeAg-positive		HBeAg-negative	
	Lamivudine n = 455	**Telbivudine n = 445**	**Lamivudine n = 232**	**Telbivudine n = 235**
ALT flare category	%	%	%	%
Grade 1: ALT ≥ 2 x Baseline & ≥ 2 x ULN[1]	6.6	7.6	1.7	1.3
Grade 2: ALT ≥ 3 x Baseline & ≥ 3 x ULN	2.4	3.1	0	0
Grade 3: ALT ≥ 500 IU/l & ≥ 2 x Baseline	3.5	3.1	0.4	0.9
Grade 4: ALT ≥ 2 x Baseline & bilirubin ≥ 2 x Baseline & ≥ 2 x ULN	0	0	0	0
Total to end of week 24	12.5	13.9	2.2	2.1

[1] *ULN: Upper limit of normal*

[2] *Includes ALT flares that occurred after the first dose and before or during week 24.*

Table 25: Analysis of categories of on-treatment ALT flares week 24 to week 52[2]

	HBeAg-positive		HBeAg-negative	
	Lamivudine n = 455	**Telbivudine n = 445**	**Lamivudine n = 232**	**Telbivudine n = 235**
ALT flare category	%	%	%	%
Grade 1: ALT ≥ 2 x Baseline & ≥ 2 x ULN[1]	1.1	0.4	0.9	0
Grade 2: ALT ≥ 3 x Baseline & ≥ 3 x ULN	1.1	0.2	3.4	0
Grade 3: ALT ≥ 500 IU/l & ≥ 2 x Baseline	1.5	0.2	0.4	0
Grade 4: ALT ≥ 2 x Baseline & bilirubin ≥ 2 x Baseline & ≥ 2 x ULN	0.7	0	0	0
Total week 24 to week 52	4.4	0.9	4.7	0

[1] *ULN: Upper limit of normal*

[2] *Includes ALT flares that occurred after week 24 and before or during week 52.*

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

No non-RCT trials have studied telbivudine efficacy and therefore no evidence from non-RCT trials can be presented.

5.8.1 Critical appraisal of relevant non-RCTs

- How was allocation concealed?
- What randomisation technique was used?
- Was a justification of the sample size provided?
- Was follow-up adequate?
- Were the individuals undertaking the outcomes assessment aware of allocation?
- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.
- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?
- How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.
- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?
- Were the study groups comparable?
- Were the statistical analyses used appropriate?
- Was an intention-to-treat analysis undertaken?
- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

5.8.2 Results of the relevant non- RCTs

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence from the pivotal study, GLOBE [47], demonstrates the significant benefits of telbivudine on the key outcomes of interest in the treatment of CHB.
Chronic hepatitis B is a lifelong condition with serious clinical consequences that evolve over many years. Active disease progression ultimately leads to liver inflammation with associated morbidity, cirrhosis, decompensated liver failure, hepatocellular carcinoma and death. Few of these sequelae are appropriate for study in the setting of clinical trials, and indeed data from studies exceeding 5 years duration are rare. Therefore interventional trials invariably rely on surrogate endpoints (eg viral DNA levels; seroconversion) together with more direct evidence of disease activity and progression, namely ALT elevation, histologic evidence of inflammation and fibrosis. The correlation of both surrogate and direct measures with disease progression and outcomes has been determined in long-term observational studies with conclusive results [48, 49]. Thus HBV DNA is widely accepted as a surrogate for disease activity and an elevated viral load as a predictor of acute inflammation, progressive liver pathology and the consequent risks of fibrosis, cirrhosis and hepatocellular carcinoma.
In summary, although the incidence of serious complications of CHB was low in the 2 year GLOBE study itself, the endpoints that were evaluated in the trial are internationally recognised as valid predictors of clinical outcome.

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

In common with many clinical trials, the GLOBE study is likely to have required greater monitoring of patients than would be the case in usual clinical practice. Patients would have attended clinics more frequently, and had more tests conducted than would normally be the case, In addition, it is unlikely that patients would undergo a routine biopsy at 1 year as occurred in the trial, Instead, it is expected that biopsies would only occur to confirm suspected progression of disease.

The licensed dose (600 mg o.d.) was the dose used in the GLOBE study.

HBV DNA as a marker of clinical outcome

Although the GLOBE study does not directly address the question of whether sequential or combination therapy is the most cost-effective approach to maintain the efficacy of antiviral treatment over the longer term, it does provide evidence for 24-week HBV DNA as an early predictive marker of treatment success (including e seroconversion as above) on nucleoside monotherapy. The study thus suggests a rational approach to patient selection for additional intervention (eg addition of a nucleotide) on the basis of incompletely suppressed HBV at the 24-week point, which is shown to be predictive of subsequent resistance [1].

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in Appendix 3, Section 9.3.

No formal search of the cost-effectiveness literatures was undertaken regarding treatments for Hepatitis B. This decision was taken in light of the recent review of Lamivudine, Adefovir Dipivoxil and Peginterferon Alfa-2a conducted by NICE, [50] which was used as the initial gold standard for economic evaluations relevant to England and Wales. The assessment report is available from the NICE website [51] and has been published as an HTA report [12].

In addition to data contained within this report, [12] data from an ongoing RCT (GLOBE [46]) have been used. The GLOBE trial evaluates the clinical effectiveness of both lamivudine and telbivudine in the treatment of Chronic Hepatitis B. It was a single treatment trial. Patients who developed resistance, as defined in the protocol, were removed from the trial. The trial was selected because it was a large head to head trial of Telbivudine versus Lamivudine, which is the current recommended first-line treatment option for those patients who are intolerant to Peginterferon Alfa-2a.

There were 1,367 patients enrolled of whom 921 were HBeAg-positive. Of these, 458 patients were randomised to Telbivudine and 463 patients to lamivudine. In the HBeAG-negative ITT patient population there were 446 patients, of whom 222 patients were randomised to Telbivudine and 224 patients to lamivudine. As will be described later, only patients that reached a treatment criterion of having twice the upper normal level of ALT have been used in the modelling. In the HBeAg-positive cohort, 588 out 921 had ≥2-fold ALT elevation and in the HBeAg-negative cohort, 255 out of 446 had ≥2-fold ALT elevation. Where data were missing for patients they have been excluded from the analyses that calculated transition rates.

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

The economic analysis selected has great relevance to decision making in England and Wales as it was used as data by the NICE appraisal committee. Incremental analyses indicated that, for patients who were intolerant of Peginterferon Alfa-2a, the most cost-effective algorithm would be to prescribe Lamivudine followed by Adefovir Dipivoxil for

patients who become resistant to Lamivudine.

The methodology undertaken in the HTA report [12] was that of a transition state model that focussed on seroconversion of the disease. This approach is entirely based on observations from HBeAG-positive patients and may not be relevant for patients with HBeAG-negative disease since by definition patients who are eAg-negative cannot seroconvert because they do not have the antigen to lose. In view of the differences between eAg positive and eAg negative disease, in terms of the demographics, epidemiology and natural history of the two conditions, the seroconversion model has limitations. It is believed that modelling approaches based on the viral load of a patient (i.e. HBV DNA) could form a more accurate model. In chronic hepatitis B a high viral load is a prognostic factor for morbidity and mortality from hepatocellular carcinoma and chronic liver disease. Chen, G. *et al [49]* A strong relationship has also been established between the viral load and the probability of future cirrhosis and hepatocellular carcinoma. Chen, C. *et al [48]*

6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2
Perspective costs	NHS and Personal Social Services	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of economic evaluation	Cost-effectiveness analysis	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	Quality-adjusted life years (QALYs)	5.5
Health states for QALY measurement	Described using a standardised and validated instrument	5.5
Benefit valuation	Time trade-off or standard gamble	5.5

Source of preference data **Discount rate**	Sample of public Health benefits and costs – both 3.5%	5.5 5.7.2
Equity	No additional weighting to QALYs	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

Note:

Two models are provided; a seroconversion model and a viral load model. The seroconversion model which replicated the approach used in the previous NICE assessment was applicable to HBeAg-positive patients only whereas the viral load model simulates both patients with HBeAg-positive disease and those with HBeAg-negative disease. The viral load approach is our favoured methodology however we have attempted to replicate the seroconversion model that provided data for the previous NICE assessment so that the results produced by the two methodologies can be compared. Both models are built in Excel 2003 (using the latest service packs) and utilise a transition state approach. The time cycle for the viral load model was 6 months, whilst this value was set to 1 year for the seroconversion model.

In describing the methodology, parameters and data used we will specifically indicate which model is being discussed.

6.2.1 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.

Telbivudine is assumed to be a treatment option for patients with Hepatitis B that are intolerant of Peginterferon Alfa-2a. Both models assume that telbivudine is given as monotherapy at a dose of 600 mg once daily. The treatment duration is lifelong but discontinuation in each model is as follows:

In the viral load model all patients, regardless of whether they are HBeAg-positive or HBeAg-negative, will continue to receive treatment until they seroconvert the surface antigen and cure the disease, develop decompensated cirrhosis, hepatocellular carcinoma or undergo liver transplantation or develop resistance to the antiviral.

In the seroconversion model patients will continue to receive treatment until they seroconvert the surface antigen and cure the disease or develop resistance to the treatment they were prescribed. Additionally patients will discontinue treatment six months after seroconverting the e antigen and entering the inactive carrier (HBsAg+, HBeAg-) health state.

6.2.2 Patients

6.2.2.1 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 economic evaluation analyses patients with Hepatitis B that have ALT levels at 2 times the upper level of normal, which is the standard criterion for treatment ((AASLD, APASL and EASL).

6.2.2.2 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?

The analyses were conducted only for those patients that have ALT levels at 2 times the upper level of normal. Patients with lower ALT levels were excluded as it was deemed that these would not be routinely treated in England and Wales. Further subgrouping was undertaken by dividing patients into those with e-positive disease and those with e-negative disease. This distinction was necessary due to the different age and sex distributions of patients diagnosed with hepatitis B, in addition to fundamental differences between the diseases.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

To our knowledge no relevant subgroups have been omitted

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

For both models, patients enter on diagnoses of chronic Hepatitis B and after initial use of Peginterferon Alfa-2a, where appropriate. Patients exit the evaluation on death, either related to the disease or through other causes. Note that patients may not be on active treatment throughout the entire modelling period if they either become resistant to all interventions or are perceived to be cured.

6.2.3 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 (Section A).

Comparator drugs are lamivudine and adefovir dipivoxil, which were both included in the NICE assessment, and the recently marketed entecavir, which was not. Lamivudine and adefovir dipivoxil have been explicitly modelled alongside telbivudine in the seroconversion model. Only lamivudine has been modelled in the viral load model. Due

to insufficient data entecavir has not been formally modelled. However a mixed treatment comparison has been conducted that shows that there is no significant difference in the rates of histologic improvement, the proportion of patients with undetectable HBV DNA, the rates of ALT normalisation, seroconversion and loss of HBeAg between telbivudine and entecavir. This is detailed in Appendix A. As telbivudine is less expensive than entecavir (£3787and £4602 respectively per annum) and there are no significant differences in the key outcome measures, telbivudine has been assumed to be the more cost-effective intervention.

It is impossible to compare, even indirectly, the resistance rates of telbivudine and entecavir at 2 years, because the data reported for entecavir at 2 years is not based upon the ITT population; only a subset of patients who commenced the study (69% of HBeAg-positive and 15% of HBeAg-negative patients) were allowed to continue therapy beyond 52 weeks and were followed-up to 2 years. The authors of the 2 year Entecavir paper [27] have summarised the limitations of their study design in the discussion section as follows:

> *The study was designed to evaluate the possibility of discontinuing treatment after meeting prespecified patient management criteria at week 52; therefore, the protocol specified that responders and nonresponders should discontinue treatment at or after week 52. As a result, another challenge when interpreting the second-year results derives from the absence of a cross-sectional presentation of response rates at week 96.* ***After week 52, it is not possible to provide an assessment in which all patients who originally started treatment are accounted for at a single time point under uniform treatment conditions. Therefore, the results from this study cannot be compared directly with other studies that evaluate continuous treatment in all patients through 2 years****, regardless of clinical course....*

6.2.4 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 study perspective is that of the NICE reference case.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

In both models the time horizon was set at a sufficient duration to capture all the costs and QALYs gained throughout a patient's lifetime. For example, the time horizon was 100 years for the seroconversion model.

Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.5.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

Each model structure will be discussed independently.

<u>The structure of the viral load model.</u>

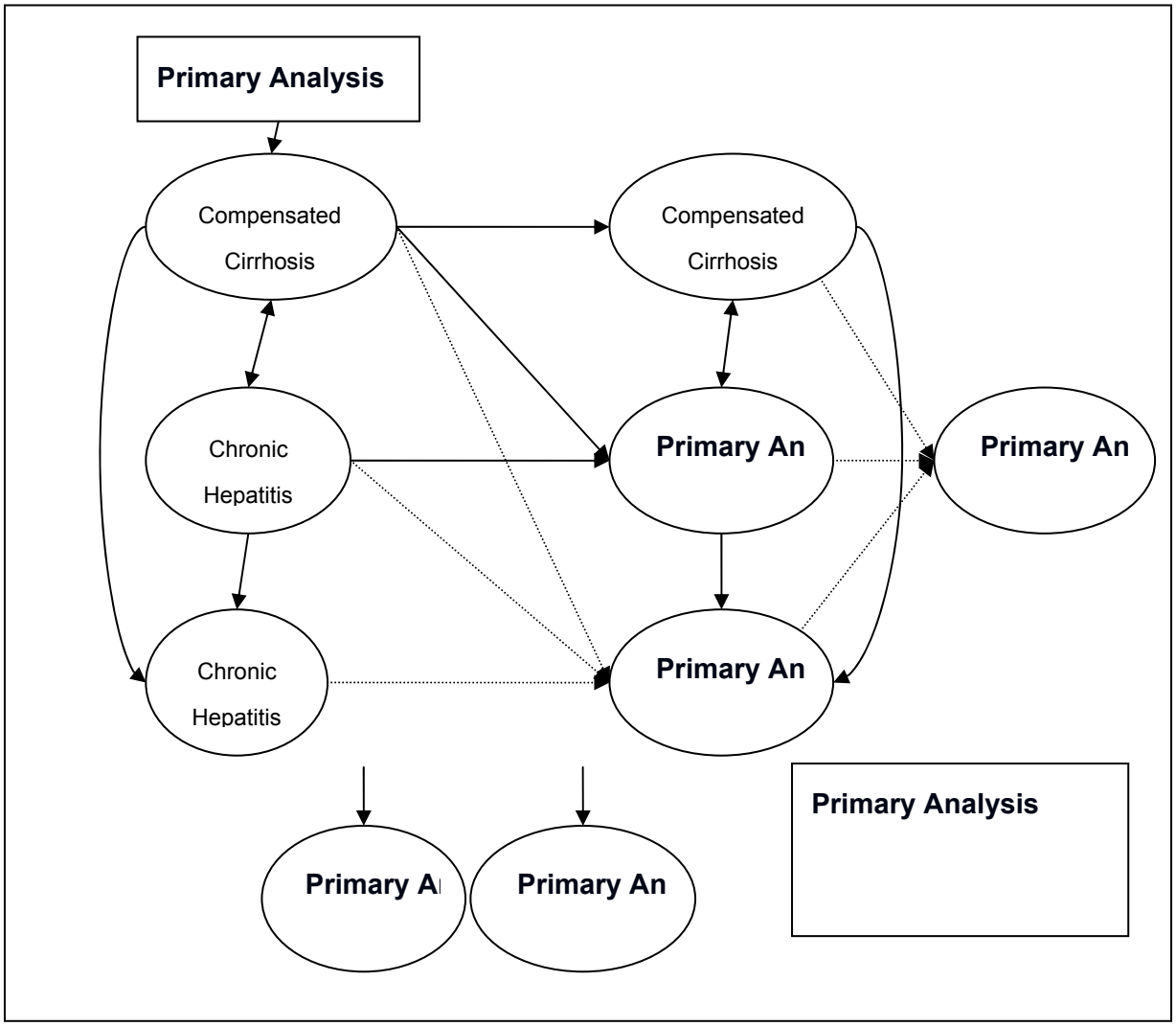
The viral load model simulates the experiences of a hypothetical cohort of patients who have recently been diagnosed as suffering from chronic hepatitis B. The model differentiates between patients with e antigen (HBeAg)-positive chronic hepatitis B and those with e antigen negative (HBeAg)-negative chronic hepatitis B due to the differing epidemiology of the two diseases. Both cohorts of patients are either unwilling or unable to take an Interferon and are about to start treatment with either Lamivudine or Telbivudine

Patients suffering from e antigen (HBeAg)-positive chronic hepatitis B will be in one of the following health states:

1. Chronic hepatitis, surface antigen positive and e antigen positive.
2. Chronic hepatitis, surface antigen positive and ‘e antigen negative.
3. Chronic hepatitis, surface antigen negative and e antigen negative.
4. Compensated cirrhosis, surface antigen positive and ‘e antigen positive.
5. Compensated cirrhosis, surface antigen positive and e antigen negative
6. Compensated cirrhosis, surface antigen negative and e antigen negative.
7. Decompensated cirrhosis.
8. Hepatocellular carcinoma.
9. Post Liver Transplant
10. Dead.

A schematic of the viral load model for patients suffering from e antigen (HBeAg)-positive chronic hepatitis B is shown in Figure 5.

Figure 5: Allowable health states and transitions from e antigen (HBeAg)-positive chronic hepatitis B.

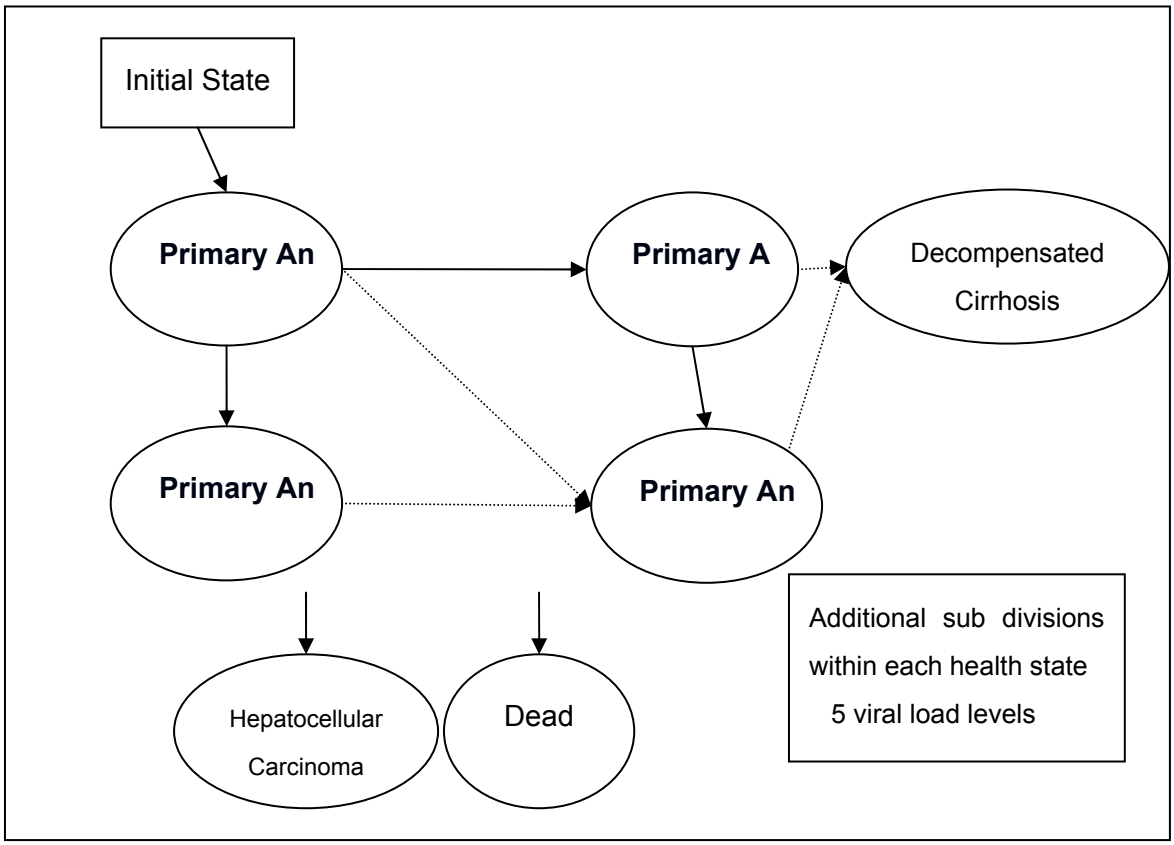


Patients suffering from e antigen (HBeAg)-negative chronic hepatitis B will be in one of the following health states:

1. Chronic hepatitis, surface antigen positive and ‘e antigen negative.
2. Chronic hepatitis, surface antigen negative and e antigen negative.
3. Compensated cirrhosis, surface antigen positive and e antigen negative
4. Compensated cirrhosis, surface antigen negative and e antigen negative.
5. Decompensated cirrhosis.
6. Hepatocellular carcinoma.
7. Post Liver Transplant
8. Dead.

A schematic of the viral load model for patients suffering from e antigen negative (HBeAg)-negative chronic hepatitis B is shown in Figure 6.

Figure 6: Allowable health states and transitions from e antigen (HBeAg)-negative chronic hepatitis B.



In addition, within these health states patients are subdivided into their viral load level, whether they have liver transplant, and whether they are resistant to the drug. The different characteristics are:

Serological markers
- Surface antigen positive and e antigen positive (HBsAg+, HBeAg+)
- Surface antigen positive and e antigen negative (HBsAg+. HBeAg-)
- Surface antigen negative and e antigen negative (HBsAg-, HBeAg-)

DNA viral level
- Viral level 1: Less than 300 copies per millilitre
- Viral Level 2: Between 300 and 9,999 copies per millilitre
- Viral Level 3: Between 10,000 and 99,999 copies per millilitre
- Viral Level 4: Between 100,000 and 999,999 copies per millilitre
- Viral Level 5: One million copies or greater per millilitre

Histology
- Chronic hepatitis
- Cirrhosis

Antiviral drug resistance
- Resistant to treatment
- Not resistant to treatment

Clinical descriptors
- Decompensated cirrhosis

Liver transplant
Hepatocellular carcinoma

Where resistance to either lamivudine or telbivudine has occurred, the patient is provided with best supportive care (BSC) only (although in clinical practice these patients are likely to be offered adefovir dipivoxil. These patients are then assumed to regress to viral level 5 as observed in such patients within the GLOBE trial [46].

The structure of the seroconversion model.

The model simulates the experiences of a hypothetical cohort of patients who have recently been diagnosed with e antigen positive chronic hepatitis B who are unwilling or unable to take an Interferon and are about to start treatment with one of Telbivudine, Lamivudine or Adefovir Dipivoxil. The model includes eight health states, specified below, with patients moving between these states according to specific transition probabilities.

1. Cured (HBeAG-negative and HBsAg negative).
2. Inactive Carrier (HBsAg positive and HBeAG-negative).
3. Chronic Hepatitis B.
4. Compensated Cirrhosis.
5. Decompensated Cirrhosis.
6. Hepatocellular Carcinoma.
7. Liver Transplant Year 1 (in the year of transplantation).
8. Liver Transplant Year 2+ (subsequently).

Two additional absorbing health states have been included. These are chronic hepatitis B-related death and death through non-chronic hepatitis B causes.

A schematic of the seroconversion model is shown in Figure 7.

In the figure, the inactive carrier health state refers to patients who retain the surface antigen but have seroconverted the e antigen. The cured heath state refers to patients who have seroconverted both the surface antigen and the e antigen.

The natural death (or non-chronic hepatitis B related death) state is not shown in the figure for clarity. Patients are able to remain in any health state, however, these transitions have not been shown in order to aid clarity of the possible interstate transition.

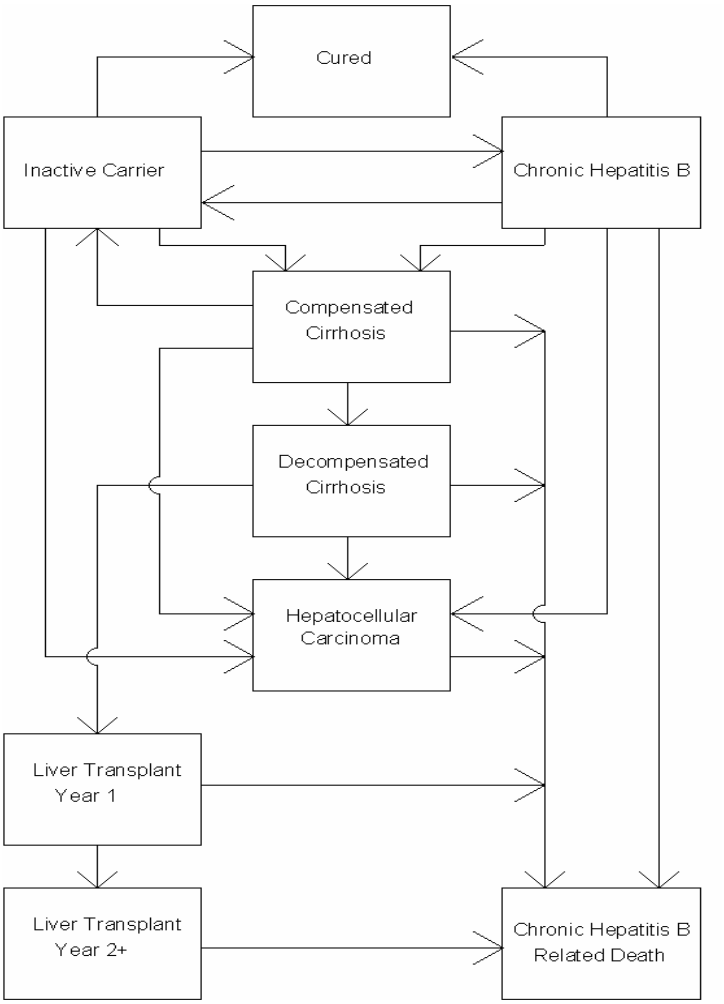
The possibility of drug resistance has also not been shown in the figure to aid clarity.

The following assumptions were made:

1. Resistance cannot develop in patients who move to the inactive carrier health state in the same cycle.

2. Resistance does not develop in patients who remain in the inactive carrier health state.

Figure 7: Allowable health states and transitions for the seroconversion model.



There is a very small probability of movement from Cured to Hepatocellular Carcinoma (mean probability 0.0005 Wong et al [52]). This transition has been omitted from the diagram for clarity reasons.

Model population

Where possible, both models have been populated using data taken from the GLOBE trial [46]. However, since the GLOBE study has only two years of follow up data, there have been no observed severe events, such as hepatocellular carcinoma. In circumstances where there is no data we have taken the values provided in the HTA report [12].

We have used the population characteristics reported in the HTA report [12]. Thus the HBeAg-positive CHB patient cohort will have a mean age at diagnosis of 31 years, with the standard deviation around this mean assumed to be one year, and that 75% of this cohort will be male.

The HBeAg-negative CHB patient cohort will have a mean age at diagnosis of 40 years, with the standard deviation around this mean age assumed to be one year, and 90% of this cohort will be male.

For the viral load model, the distribution of patients between the specific viral loads at the start of treatment is taken from the GLOBE study. For patients with e antigen (HBeAg)-positive CHB; viral load 1, 0.0%; viral load 2, 0.2%; viral load 3, 0.8%; viral load 4, 3.5%; viral load 5, 95.5%. For patients with e antigen (HBeAg)-negative CHB; viral load 1, 0.0%; viral load 2, 0.9%; viral load 3, 3.0%; viral load 4, 11.0%; viral load 5, 85.1%.

	HBeAg-postive patients	**HBeAg-negative patients**
Viral Load 1	0.0	0.0
Viral Load 2	0.2	0.9
Viral Load 3	0.8	3.0
Viral Load 4	3.5	11.0
Viral Load 5	95.5	85.1

In the seroconversion model all patients begin in the chronic hepatitis B state.

Transition probabilities calculated for the viral load model.

The distribution of patients between viral load levels at the start of the model has also been taken from GLOBE data [46].

The probabilities of moving between viral load levels in each of the first 4 six-month cycles have been taken directly from that observed in the GLOBE trial [46]. The transition probabilities observed in the period between 18 months and 24 months have been assumed to continue indefinitely.

Depending on their viral level, patients in the positive disease cohort may lose the e antigen, lose the surface antigen (if they have previously lost the e antigen) or experience reactivation of the disease (if they have previously lost the e antigen but not lost the surface antigen). It is permissible for patients to lose both the e and surface antigen in the same transition period. Patients with low viral load levels have a higher probability of losing serological markers and normalising their ALT levels than patients with higher viral load levels. Data on these transitions are contained in Appendix B.

Adjusting the transition probabilities taken from the GLOBE trial due to sparse data.

Due to the large number of combinations of time period, viral load levels, resistance status and underlying disease progression, a number of raw transition probabilities were zero as they were no observed occurrences. Leaving these cells as zero would imply that such transitions were impossible, which may not be justifiable. Potential corrections to the transition probabilities include fitting distributions through the known data or eliciting likely probabilities from clinicians - although both of these approaches would require significant time and resources, and would also be open to question. An alternative approach is to add a number (typically 0.5 or 1) to all transitions where there was one or more possible transitions with zero observations. The effect of this non-informative prior is more pronounced when data are scarce: For example, assuming a Boolean transition state with only 1 data point, which moved to state 1, the unadjusted risk would be 100% and 0%. With the addition of 0.5, the number would be assumed to be 1.5 and 0.5 changing the probabilities to 75% and 25%. If there were 100 data points all of which has transited to state 1, the adjusted probabilities would become 99.5% and 0.5% (associated with numbers of 100.5 and 0.5).

The use of the same non-informative prior for all transitions where one or more possible transitions had zero elements could potentially bias the results. For example, assume that no transitions were observed for non-resistant patients in viral load level 2 to viral load levels 3, 4 or 5. Using a non-informative prior (in this case 0.5) would give the same probability of the patient moving to viral load level 3 as to viral load level 5, which is clinically implausible.

The value of the non-informative prior is relatively arbitrary but we have considered that 0.5 is a bound on the results; due to the relatively large number of transition states (all associated with increased severity of viral load) that have zero observations. We have further assumed that using a non-informative prior of 0.0 (i.e. leaving the data unchanged) would represent the other bound on the results. The true cost-effectiveness of Telbivudine versus Lamivudine has thus been assumed to lie between the values produced by these two scenarios. Due to the time taken for the viral load model to generate sufficient results for a formal PSA analyses (over a week of computational time) in-depth analyses using different non-informative priors has not been undertaken.

The exception to adding a non-informative prior was for the transition probabilities between levels of viral load in the first six months of treatment (for either telbivudine or lamivudine). These transition probabilities were considered inappropriate to be adjusted as we assumed, with clinical input, that it would be extremely unlikely for non-resistant patients to worsen their viral load level during this time, and it was these cells that contained the zero observations.

The relationships between viral load level, age, gender and ALT levels and the risk of developing compensated cirrhosis and the probability of developing hepatocellular carcinoma were estimated from Taiwanese data [28, 48]. These studies had 3,653 participants followed for a mean of 11.4 years and formulated Cox proportional hazard models to estimate the risks of developing compensated cirrhosis and the probability of developing hepatocellular carcinoma. As all patients in each combination of health state and viral load level were considered homogenous this fitted a transition state model. These risk equations did not originally include time varying constants and thus the risks would not increase as patients became older, nor did these risk coefficients allow the presence of compensated cirrhosis to effect the risk of hepatocellular carcinoma. This was considered a

weakness and the formulae were adjusted to incorporate these factors, but were then re-calibrated in order that the average probability of compensated cirrhosis and hepatocellular carcinoma was still equal to that seen in the Taiwanese data [28, 48]. The formulae, which were calculated by Dr John Wong, used to predict the risks of compensated cirrhosis and hepatocellular carcinoma are provided in Appendix C.

Patients without cirrhosis may develop compensated cirrhosis and those with compensated cirrhosis may develop decompensated cirrhosis. Once decompensated cirrhosis develops, patients may undergo liver transplantation. Patients with decompensated cirrhosis are at an increased annual probability of mortality, as are patients who have had a liver transplant.

Since data from the GLOBE trial are only available for the initial two years of treatment, few data are available regarding the annual probability of viral related death from decompensated cirrhosis, hepatocellular carcinoma or liver transplantation. Similarly few data are available regarding the annual probability of progressing from compensated cirrhosis to decompensated cirrhosis or the annual probability of receiving liver transplantation in patients with decompensated cirrhosis or the annual probability of receiving liver transplantation patients in the initial six months or the development of hepatocellular carcinoma. For these parameters, data have been taken from the HTA report [12]. Within the HTA report [12] there were a number of parameters that were assumed to have constant value for both lamivudine and adefovir dipivoxil. We have assumed that there is a class effect and that these values can also be applied to telbivudine.

Details of the variables used in the viral load model together with details their mean values and distributions is presented in Appendix B. A separate list of the assumptions used in the viral load model is presented in Appendix D.

Transition probabilities calculated for the seroconversion model.

The values for parameters were taken from the HTA report [12] excluding the probability of loss of e antigen, surface antigen, the probability of becoming resistant to drug and the reactivation of disease. These probabilities were estimated for telbivudine and lamivudine directly from GLOBE data [46]. However since neither adefovir dipivoxil nor best supportive care were included in the GLOBE trial [46] parameters associated with these interventions needed to be estimated.

For adefovir dipivoxil the rates of losing e antigen and losing surface antigen were the same as lamivudine in the HTA report [12]. We have assumed that the rate of e antigen loss and surface antigen loss for adefovir dipivoxil would be equal to the mean value of those estimated for lamivudine and telbivudine within the model.

In the HTA report [12] adefovir dipivoxil was assumed better at preventing reactivation than lamivudine, and we have used this relationship to estimate the re-activation rate on adefovir dipivoxil. The following formula was assumed to estimate the reactivation rate associated with adefovir dipivoxil.

$$P_{assumed}(Adefovir\ Dipivoxil) = \left(\frac{P_{\mathrm{mod}}(Lamivudine) + P_{\mathrm{mod}}(Telbivudine)}{2}\right) * \left(\frac{P_{HTA}(Adefovir\ Dipivoxil)}{P_{HTA}(Lamivudine)}\right)$$

The proportion of patients who become resistant to adefovir dipivoxil was assumed to equal those values used in the HTA report [12].

For BSC the reactivation rate was assumed to equal the distribution used in the HTA report [12]. For estimating the rate of both the loss of surface antigen and e antigen the following methodology was applied. The value used in the model was set to the lowest value from the value sampled from the distribution contained in the HTA report [12] and the sampled values for telbivudine and lamivudine estimated within the model. This methodology was used as it ensured that the rates of beneficial transitions were not higher on BSC than on any of the active interventions. This approach may over-estimate the benefit of BSC, which is expected to favour lamivudine rather than telbivudine as the former drug has the greater resistance rate and would be expected to have a greater proportion of patients on BSC at a specific time period. It was assumed that patients could not become resistant to BSC.

Note:

We have assumed that the first antiviral treatment used in an algorithm has an impact on reducing the probability of compensated cirrhosis developing in the first year of treatment, not just lamivudine as stated in the HTA report [12]. We suspect that this in an error in the reporting of the HTA modelling methodology and this is covered in more detail in Appendix E.

A list of variables used in the seroconversion model together with their mean values and distributions presented in Appendix F. A separate list of the assumptions used in the seroconversion model is presented in Appendix G.

6.2.5.2 Why was this particular type of model used?

A transition state model was deemed appropriate as there are a number of discrete health states which are mutually exclusive and exhaustive.

6.2.5.3 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 transition state model allowed the key characteristics of the model to be incorporated without undue complexity. Additionally this was the structure chosen by the assessment group in the previous NICE assessment [51] which allowed results to be compared without introducing potential differences due to modelling methodologies. Scarce data precluded discrete event simulation, whilst the lack of interaction between patient history and future event meant that individual patient modelling was not necessary. For the seroconversion model there was no choice regarding the model structure as we were attempting to replicate previous work, although a different platform was used.

6.2.5.4 What were the sources of information used to develop and inform the structure of the model?

For both models the model was populated with data from the GLOBE trial and from a recent HTA report [12, 46].

6.2.5.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

As far as we are aware, all essential features and conditions have been included in the model.

6.2.5.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

For the seroconversion model we adopted the yearly time cycle used in the assessment group model [51]. For the viral load model we shortened the time cycle to allow the potential for more frequent movement between health states. Six months was deemed an appropriate period given the rates of transition seen in the literature.

6.2.5.7 Was a half-cycle correction used in the model? If not, why not?

Half cycle correction was included in both the viral load and seroconversion models. Note that the time cycle is 6 months for the viral load and 1 year for the seroconversion model.

6.2.5.8 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 difference in effectiveness between the technology and its comparator?

The GLOBE trial [46] has collected currently only 2 years' worth of data. Thus any calculations of costs and benefits during a patient's lifetime (the recommended time horizon) require extrapolation of the data. We have assumed that the calculated transition rates relating to the last cycle (18-24 months for the viral load model and 1-2 years for the seroconversion model) are applicable to all remaining cycles, which is the assumption used in the HTA report [12]. This assumption was made for each intervention analysed.

b) Non-model-based economic evaluations

6.2.5.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

N/A

6.2.5.10 Provide details of the clinical trial, including the rationale for its selection.

N/A

6.2.5.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

N/A

6.2.5.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of

the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

N/A

6.2.5.13 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 any longer-term differences in effectiveness between the technology and its comparator?

N/A

6.2.6 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.6.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

In the viral load model it was assumed that patients who did not receive treatment would have disease progression equal to patients in the most severe viral load state.

In the seroconversion model the baseline risk was assumed to be that associated with BSC, which assumes no active intervention. The progression rates associated with the baseline were taken from the HTA report [12] unless these were sampled to be better than an active treatment. The adjustments of progression rates in such circumstances have been previously discussed.

6.2.6.2 How were the relative risks of disease progression estimated?

For telbivudine and lamivudine the absolute transition probabilities were taken from GLOBE.[Error! Bookmark not defined.] For adefovir dipivoxil and BSC, which were not included in the GLOBE trial,[Error! Bookmark not defined.] the rates were estimated using the methodology previously described.

6.2.6.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Extrapolating beyond the length of RCT evidence was necessary. In the Viral load model the level of viral load was linked to progression to more severe disease states, such as compensated cirrhosis or hepatocellular carcinoma. These transition probabilities were adjustments of those presented in published papers [28, 48] and are detailed in Appendix B. The rates of viral load transition in the period 18-24 months were assumed to remain constant for a patient's lifetime.

In the seroconversion model we replicated the disease progression from the HTA report, [12] which assumed constant transition matrices across a patient lifetime once data were no longer available.

6.2.6.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Given the mode of administration (a single pill is taken per day for all interventions) and the lack of reported side effects, it was considered appropriate to exclude any non hepatitis B related health effects.

6.2.6.5 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?

We believe that the beneficial effect assumed for lamivudine in the initial cycle for the probability of progressing from chronic hepatitis B to compensated cirrhosis in the HTA report, [12] was also assumed applicable for adefovir dipivoxil, even though it was stated that this did not happen. (see Appendix E). We asked a clinical advisor whether there was a biological reason why this benefit would only apply to lamivudine and not other antiviral treatments and the answer was there was not. Hence this effect was applied to both adefovir dipivoxil and telbivudine. It is noted that the effect would only apply to the first of these three interventions used in an algorithm and not all three.
When adding non-informative priors for the viral load model it was also assumed impossible for the viral load level to increase in the first 6-month period. This hypothesis was put to our clinical expert who deemed it an appropriate assumption.

6.2.6.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

We have assumed that there will be different resource implications for those patients who lose the e antigen depending on the modelling approach adopted. In the seroconversion model we have followed the previous work and gave a further 6 months of treatment to those patients who lost the e antigen. In the viral load model we changed this assumption to one believed more appropriate and assumed that these patients remain on treatment indefinitely unless they seroconvert the surface antigen and cure the disease, develop decompensated cirrhosis, hepatocellular carcinoma or undergo liver transplantation or develop resistance to the antiviral.
No further assumptions were made over and above those contained in the HTA report. We have assumed that the assumptions in that document were reasonable due to the peer review process.

6.2.7 Measurement and valuation of health effects

6.2.7.1 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.

Only health effects associated with hepatitis B were measured, with the HTA report used as the basis for the chosen mutually exclusive states. These health states were Cured (HBeAg-, HBsAg-), Inactive Carrier (HBeAg-, HBsAg+), Chronic Hepatitis B, Compensated Cirrhosis, Decompensated Cirrhosis, Hepatocellular Carcinoma, Liver Transplant (both in initial and subsequent years) and death. Whilst the viral load model characterises patients by the level of viral load, these groups do not influence directly a patient's utility, but do so when the patients move into a designated health state.

6.2.7.2 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?

The health states listed above were valued.

In the seroconversion model the utility decrements given in the HTA report were used. However, the viral load model was constructed in a manner that required utility multipliers rather than decrements. We have conservatively assumed that the multiplier can be calculated as 1 minus the utility decrement given in the HTA report [12]. For patients who do not have an underlying utility of 1, this will have the effect of reducing the utility losses associated with health states and will be favourable to lamivudine and unfavourable to telbivudine.

6.2.7.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

The approach taken was consistent with the reference case.

6.2.7.4 Were any health effects excluded from the analysis? If so, why were they excluded?

We are aware of no reported health effects that were excluded from the analyses.

6.2.7.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed using QALYs.

6.2.8 Resource identification, measurement and valuation

6.2.8.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Examination regimes were taken from the HTA report [12] and were assumed to be higher for patients on active treatment than those not. Details of these resources are presented in Appendix H. In addition pre-treatment evaluations, taken from the HTA report [12] were included in the seroconversion model, but not the viral load model. Details of these resources are presented in Appendix I.

6.2.8.2 How were the resources measured?

Examination regimes were taken from the HTA report [12]. Details of these resources are presented in Appendix H. Details of pre-treatment evaluations are presented in Appendix I.

6.2.8.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes

6.2.8.4 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).

It was assumed that the costs of care associated with each health state remained constant throughout the model, as continual treatment (where appropriate) was required. It is noted that when active treatment is withdrawn and the patient receives BSC only,

the costs of examination are reduced.

6.2.8.5 What source(s) of information were used to value the resources?

We have assumed that the costs presented in the HTA report [12] are relevant and that these costs were in the financial year 2003/4. These costs have been inflated to 2005/6 costs, using inflation indices given in Curtis and Netten [53].

6.2.8.6 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?

The annual costs for each intervention have been obtained from the BNF [54] as follows: Lamivudine (Zeffix), £1,018.66; Telbivudine (Sebivo), £3,787.25; Adefovir Dipivoxil (Hepsera), £3,835.13.

6.2.8.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

All costs were valued consistently with the reference case.

6.2.8.8 Were resource values indexed to the current price year?

The financial year of the assessment is 2005/2006 as this was the last year with confirmed inflation indices in Curtis and Netton [53].

6.2.8.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

All costs were taken from the recent HTA report [12] and were assumed correct once inflated. The exact fiscal year of the original estimates was not clearly defined, although the level of inaccuracy that may be introduced by inappropriately identifying the financial year of the HTA report [12] is unlikely to substantially change the conclusions.

6.2.9 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, both health benefits and costs have been discounted at 3.5% per annum.

6.2.10 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.

6.2.10.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

Distributions were fitted to parameters based on published literature estimates and these were varied in PSA. Details are presented in Appendices A and B (viral load model) and Appendices D and E (seroconversion model).

6.2.10.2 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'.

PSA was undertaken. The distributions for each parameter are presented in Appendix B (viral load model) and Appendix F (seroconversion model).

Further assessment of uncertainty was addressed in the viral load model by the use of 2 non-informative priors, which did influence the results. Using the same value for movement across viral load levels could be seen as clinically incorrect, as the probability of moving to significantly more severe states would be given the same probability as moving to marginal more severe states where no data were observed for each transition. The exact value for a prior is arbitrary and thus we present the two scenarios as likely bounds on the true ICER. The submission of two models gives a good indication of the likely variance that could be introduced by taking separate approaches.

6.2.10.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

Structural uncertainty was assessed by the use of two separate models, one which allowed the rates of disease progression to be related to the level of viral load and one that did not. The ICERs for patients with e-positive disease were relatively similar whether a seroconversion or a viral load methodology were adopted; this is the only group where comparisons can be made as it is deemed that a seroconversion model is inappropriate for patients with e-negative disease.

No analyses were undertaken assessing the impact of modelling techniques other than transition state models as this approach appeared appropriate and was the basis of previous modelling assessments for NICE [51].

6.2.11 Statistical analysis

6.2.11.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

A detailed account of translating GLOBE data [46] into transition probabilities are provided in section 1.2.5.1. This additionally discusses potential problems of extracting transition probabilities in circumstances where there are zero observed transitions between health states and characteristics.

6.2.11.2 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.

There is no *a priori* reason why the transition rates should systematically change as the

duration of the modelling is extended.

6.2.12 Validity

Describe the measures that have been undertaken in order to validate and check the model.

In the viral load approach the cox proportional hazards for hepatocellular carcinoma and cirrhosis were changed to allow the disease status and the time with disease of the patient to be incorporated in a more advanced model. (see Appendix C). These models were then calibrated to ensure that the number of patients who experienced each disease state matched that reported in the initial studies [28, 48]. The data used to populate both the viral load and seroconversion models were taken from the GLOBE trial [46] and were predicted in the initial 2 years of the model. Where a non-informative prior of 0.5 was added the results, as would be expected, did not match the study identically.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves
- scatterplots on cost-effectiveness quadrants. Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

Results from the viral load model.

The viral load model compares telbivudine followed by BSC with lamivudine followed by BSC.

The results from the viral load model were heavily dependent on the non-informative prior chosen. If we take the unadjusted data the cost per QALY of telbivudine compared with lamivudine is below £15,000 per QALY for both HBeAG-positive and HBeAg-negative patients (Table 26) If a non-informative prior of 0.5 is used the cost per QALY in HBeAg-negative patients increase to £33,000 (Table 27). We have previously discussed the limitations of assuming non-informative priors and expect that the cost per QALY for HBeAg-negative patients is likely to lie between £10,000 and £33,000.

Results are presented as Mean ICER, together with the 95% uncertainty in what value this mean could be. Additionally provided is a jackknife estimator (that removes bias associated with ratios) and allows an assessment of the 95% confidence interval of the integrated mean taken from all of the PSA runs to be undertaken. Where this uncertainty is small we can be confident that the number of runs simulated in the PSA was sufficient to provide a robust estimation of the mean cost-effectiveness.

More detailed analyses, incorporating further details such as cost-effectiveness planes

and cost-effectiveness acceptability curves, are provided in Appendix J.

Conclusions from the viral load model.

Treating patients with HBeAg-positive disease is more cost-effective with telbivudine than lamivudine. It is likely that treating patients with HBeAg-negative disease is more cost-effective with telbivudine than lamivudine as the unadjusted data provides a cost per QALY below £15,000. However we have tried to examine full uncertainty by the use of a non-informative prior, and notwithstanding the criticisms of such an approach, this increases the ratio to £33,000. Note that adefovir dipivoxil has not been included in the modelling. It is noted that in the seroconversion results that the ICER for telbivudine followed by adefovir dipivoxil compared with lamivudine followed by adefovir dipivoxil is lower than that of telbivudine alone compared with lamivudine alone, thus our results in the viral load model may be unfavourable to telbivudine.

Table 26: Results from the viral load model after the application of an uninformative prior probability distribution of 0.0. The ICER reported is that of telbivudine followed with BSC where appropriate compared with lamivudine followed by BSC where appropriate. Results presented per individual patient.

	Mean incremental costs from PSA analyses	Mean incremental QALYs from PSA analyses	Mean ICER. (95% CI)	Jackknifed ICER (95% CI of integrated values)
HBeAg-positive patients	£19,087	1.30	£14,665 (£4,345 - Dominated)	£14,660 (£14,184 - £15,136)
HBeAg-negative patients	£49,003	4.67	£10,497 (£7,980 - Dominated)	£10,497 (£10,401 - £10,592)

Table 27: Results from the viral load model after the application of an uninformative prior probability distribution of 0.5. The ICER reported is that of telbivudine followed with BSC where appropriate compared with lamivudine followed by BSC where appropriate. Results presented per individual patient.

	Mean incremental costs from PSA analyses	Mean incremental QALYs from PSA analyses	Mean ICER. (95% CI)	Jackknifed ICER (95% CI of integrated values)
HBeAg-positive patients	£12,664	1.36	£9,332 (Dominating – Dominated)	£9,321 (£8,611 - £10,031)
HBeAg-negative patients	£31,255	0.94	£33,300 (Dominating – Dominated)	£33,239 (£30,292 - £36,186)

Results from the viral load model.

A larger number of algorithms can be modelled using the seroconversion model. The algorithms analysed in this report are provided in Table 28.

Table 28: Key to treatment strategies listed in Tables 29, 30 and 31

Algorithm Number	First Line Treatment	Second Line Treatment	Third Line Treatment
0	Best supportive care	Best supportive care	Best supportive care
1	Lamivudine	Best supportive care	Best supportive care
2	Telbivudine	Best supportive care	Best supportive care
3	Adefovir Dipivoxil	Best supportive care	Best supportive care
4	Lamivudine	Adefovir Dipivoxil	Best supportive care
5	Telbivudine	Adefovir Dipivoxil	Best supportive care
6	Adefovir Dipivoxil	Lamivudine	Best supportive care
7	Adefovir Dipivoxil	Telbivudine	Best supportive care

We initially present the cost per QALY associated with algorithms 1-7 compared with algorithm 0. As these are not directly comparable we also present the net benefit of each algorithm using maximum acceptable incremental cost-effectiveness ratios (MAICER) of £20,000 and £30,000 per QALY where the numbers can be directly compared.

Table 29: **Results from the seroconversion model for HBeAg-positive patients. All Treatments compared with BSC only. Results presented per 100 patients**

	Mean incremental costs from PSA analyses	Mean incremental QALYs from PSA analyses	Mean ICER. (95% CI)	Jackknifed ICER (95% CI of integrated values)
Algorithm 1	£503,059	63.78	£7,887 (£3,924 - £16,717)	£7,887 (£7,832 - £7,942)
Algorithm 2	£1,529,867	115.96	£13,193 (£7,788 - £25,194)	£13,193 (£13,118 - £13,268)
Algorithm 3	£2,136,201	117.63	£18,160 (£11,490 - £30,160)	£18,159 (£18,073 - £18,246)
Algorithm 4	£1,667,090	113.75	£14,655 (£8,599 - £25,242)	£14,655 (£14,577 - £14,734)
Algorithm 5	£2,345,968	149.58	£15,684 (£9,491 - £28,151)	£15,684 (£15,600 - £15,768)
Algorithm 6	£2,247,279	129.17	£17,398 (£11,063 - £28,322)	£17,398 (£17,317 - £17,479)
Algorithm 7	£2,512,060	136.61	£18,388 (£11,707 - £30,357)	£18,388 (£18,302 - £18,474)

Table 30: **Results from the seroconversion model for HBeAg-positive patients. All Treatments compared with BSC only. Results presented per 100 patients and using a MAICER of £20,000 per QALY**

Algorithm strategy	Comparator strategy	PSA	Jackknife estimation		
		Classical mean	Mean	95% confidence interval	
				Lower Bound	Upper Bound
1	0	£772,620	£772,620	£765,091	£780,149
2	0	£789,341	£789,341	£777,316	£801,366
3	0	£216,498	£216,498	£205,536	£227,461
4	0	£607,985	£607,985	£596,800	£619,170
5	0	£645,573	£645,573	£630,727	£660,419
6	0	£336,147	£336,147	£324,545	£347,749
7	0	£220,220	£220,220	£207,680	£232,760
2	1	£16,721	£16,721	£6,336	£27,105

It is seen that the algorithm with the greatest mean net benefit is telbivudine followed by best supportive care. Further analyses (bottom row of the table) showed that this had a significantly higher mean net benefit than the next best strategy (which was lamivudine alone)

Table 31: Results from the seroconversion model for HBeAg-positive patients. All Treatments compared with BSC only. Results presented per 100 patients and using a MAICER of £20,000 per QALY.

Algorithm Strategy	Comparator Strategy	PSA	Jackknife Estimation		
		Classical mean	Mean	95% confidence interval	
				Lower Bound	Upper Bound
1	0	£1,410,460	£1,410,460	£1,399,592	£1,421,327
2	0	£1,948,944	£1,948,944	£1,932,001	£1,965,888
3	0	£1,392,848	£1,392,848	£1,377,608	£1,408,088
4	0	£1,745,522	£1,745,522	£1,729,984	£1,761,061
5	0	£2,141,343	£2,141,343	£2,120,997	£2,161,689
6	0	£1,627,861	£1,627,861	£1,611,759	£1,643,962
7	0	£1,586,360	£1,586,360	£1,569,159	£1,603,561
5	4	£395,821	£395,821	£382,897	£408,744

It is seen that the algorithm with the greatest mean net benefit is telbivudine followed by adefovir dipivoxil followed by best supportive care. Further analyses (bottom row of the table) showed that this had a significantly higher mean net benefit than if lamivudine were the initial drug in the algorithm.

More detailed analyses, incorporating further details such as cost-effectiveness planes and cost-effectiveness acceptability curves are provided in Appendix J.

<u>Conclusions from the seroconversion model.</u>

Treating patients with HBeAG-positive disease is more cost-effective when telbivudine is the initially prescribed drug. Whether the treatment algorithm should contain adefovir dipivoxil as a subsequent treatment should a patient become resistant to telbivudine will

depend on the MAICER assumed.

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No subgroup analyses have been conducted beyond those patients divided into HBeAg-positive and HBeAg-negative disease, all of which had ALT levels greater than 2 times the upper limit of normal. These patients formed our base case analyses.

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

Excluding the PSA analyses, only one sensitivity analysis was conducted, which was the interpretation of data sets where there was a relatively large number of potential transition with no observed data. We conducted sensitivity analyses by leaving the data unaltered and also using a non-informative prior of 0.5. Both approaches have limitations. We have assumed that these scenarios provide bounds on the cost-effectiveness ratio. Using unaltered data, the incremental cost-effectiveness ratio would generally be seen as cost-effective [55]. It is seen that the use of the non-informative prior increases the cost-effectiveness ratio to £33,000, which may be outside of acceptable cost-effectiveness ratios, [55] although there are reasons to believe this value is an overestimate since adefovir dipivoxil treatment has not been included in this model.

6.3.4 Interpretation of economic evidence

6.3.4.1 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?

There have been no previously published cost-effectiveness evaluations of telbivudine. Our seroconversion model produced similar results to those presented in the NICE report (see Appendix K).

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

This economic evaluation focuses only on those patients who are intolerant to Peginterferon Alfa-2a and who have an ALT level at greater than 2 times the upper limit of normal.

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The limitation of the viral load model is the omission of Adefovir Dipivoxil as a comparable treatment option.

The limitation of the seroconversion model is that it is informed and populated by data solely from HBeAg-positive disease.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The viral load model could be adapted to include Adefovir Dipivoxil as a comparator treatment. However, since the GLOBE phase three clinical trial only investigated the treatments Telbivudine and Lamivudine a further clinical trial would need to be performed to obtain the information on viral load progression under Adefovir Dipivoxil required by the viral load model.

Both the seroconversion and the viral load models could be adapted to include entecavir as a comparator treatment. However, no comparable literature specifying the results of a clinical trial of entecavir and some treatment common to our modelling is available at this time.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budgetary impact for the NHS in England in Wales is likely to be relatively small. We have assumed that all patients would previously have been treated with lamivudine followed by adefovir dipivoxil followed by BSC. Based on our research, we have assumed that this algorithm would be replaced by telbivudine followed by adefovir dipivoxil followed by BSC. Our results for the seroconversion model showed that the additional lifetime costs per 100 patients was approximately £700,000 (Table 1.3.1.3). If there are an expected 700 cases diagnosed every year, as indicated in Table 2 of the HTA report [12] we would expect an upper limit on the additional expenditure to be £5 million pounds per annum, assuming all patients are treated.

7.2 What number of patients were assumed to be eligible? How was this figure derived?

We have assumed that all patients who are reported to have Hepatitis B are eligible for treatment. This data has been taken from a recent HTA report [12] and is expected to be approximately 700 patients per year, which is the approximate average between 1990 and 2003.

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

For the budgetary impact analyses, we have assumed 100% uptake in treatment. The overall budgetary impact will change proportionately if a smaller percentage of patients receive the treatment.

7.4 What assumption(s) were made about market share (where relevant)?

We have assumed that every person treated would receive the most cost-effective algorithm; that of telbivudine followed by adefovir dipivoxil followed by BSC.

7.5 What unit costs were assumed? How were these calculated?

We have assumed unit costs in accordance with those presented in the description of the model.

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 daycase 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?

The expected resource use and the appropriate costs have been detailed in our model description.

7.7 Were there any estimates of resource savings? If so, what were they?

The only resource savings that have been accounted for are those associated with treatment of patients who progress to severe disease that can be averted by more efficacious treatment.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

We are unaware of further opportunities for resource savings.

8 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

1. Chalmers TC, Smith H, Blackburn B, Silverman B, Schroeder B, Reitmen D et al. (1981) Method for assessing the quality of randomised controlled trials. *Controlled Clinical Trials* 2: 31–9.

[References]

8.1 Appendix 3: search strategy for section 6

The following information should be provided.

8.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED).

[Response]

8.1.2 The date on which the search was conducted.

[Response]

8.1.3 The date span of the search.

[Response]

8.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

[Response]

8.1.5 Details of any additional searches, for example searches of company databases (include a description of each database).

[Response]

References

[1] Keeffe EB, Zeuzem S, Koff RS, et al. Report of an international workshop: roadmap for management of patients receiving oral therapy for chronic hepatitis B. Clin Gastroenterol Hepatol. 2007;5(8):890-7.

[2] Liaw,Y., Lai C, Gane,E., Hsu,C., Chen,C., and Thongsawat,S. Telbivudine GLOBE Trial: 2 Year Efficacy and Outcome Predictors in HBeAg-negative Patients with CHB. 2007;

[3] Rising Curve: Chronic Hepatitis B Infection in the UK. Hepatitis B Foundation. www.hepb.org.uk. 2007;

[4] NICE Technology Appraisal 96 (February 2006) Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B.

[5] Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. N Engl J Med 2004;350(11):1118-29.

[6] Centers of Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/b/fact.htm.

[7] Foundation for Liver Research 2004. Hepatitis B: Out of the Shadows. A report into the impact of Hepatitis B on the nation's health.

[8] WHO, Hepatitis B fact sheet WHO/204. 2007;

[9] Lee WM. Hepatitis B virus infection. N Engl J Med 1997;337(24):1733-45.

[10] GLOBE study NV-02B-007. 2007; Week 104 CSR. CONFIDENTIAL.

[11] Hou JL, Yin YK, Xu DZ, Tan D, Niu J, and Zhou XQ. A phase III comparative trial of telbivudine and lamivudine for treatment of chronic hepatitis B in Chinese patients: first-year results. 2006;

[12] Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. Health Technol Assess 2006;10(28):iii-xiv, 1.

[13] Crook PD, Jones ME, Hall AJ. Mortality of hepatitis B surface antigen-positive blood donors in England and Wales. Int J Epidemiol 2003;32(1):118-24.

[14] Brown RE, De Cock E, Colin X, Antonanzas F, Iloeje UH. Hepatitis B management costs in France, Italy, Spain, and the United Kingdom. J Clin Gastroenterol 2004;38(10 Suppl):S169-S174

[15] Hoofnagle JH. Therapy of viral hepatitis. Digestion. 1998;59(5):563-78.

[16] Lok AS, McMahon BJ. Chronic hepatitis B: AASLD Practice Guidelines. Hepatology 2007;45(2):507-39.

[17] Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of

alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Ann Intern Med 1993;119(4):312-23.

[18] Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. N Engl J Med 1990;323(5):295-301.

[19] Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005;365(9454):123-9.

[20] Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351(12):1206-17.

[21] Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341(17):1256-63.

[22] Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348(9):808-16.

[23] Hadziyannis SJ, Papatheodoridis GV, Vassilopoulos D. Treatment of HBeAg-negative chronic hepatitis B. Semin Liver Dis 2003;23(1):81-8.

[24] Schildgen O, Sirma H, Funk A, et al. Variant of hepatitis B virus with primary resistance to adefovir. N Engl J Med 2006;354(17):1807-12.

[25] Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354(10):1001-10.

[26] Tenney DJ, Rose RE, Baldick CJ, et al. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob.Agents.Chemother 2007;51(3):902-11.

[27] Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 2007;133(5):1437-44.

[28] Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130(3):678-86.

[29] Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347(3):168-74.

[30] Imperial JC. Natural history of chronic hepatitis B and C. J Gastroenterol Hepatol. 1999;14 Suppl:S1-S5

[31] Dusheiko G, Danta M. Telbivudine for the treatment of chronic hepatitis B. Drugs Today.(Barc) 2007;43(5):293-304.

[32] Lai CL, Leung N, Teo EK, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005;129(2):528-36.

[33] de Franchis R, Hadengue A, Lau G, et al. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002 Geneva, Switzerland. Consensus statement (long version). J Hepatol. 2003;39 Suppl 1:S3-25.

[34] Liaw YF, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. Liver Int 2005;25(3):472-89.

[35] Dodie Frank, XinJian Qiao, and Karin Galil. Clinical Study Report. NV-02B-007. Final report of Week 104 data. Telbivudine (SEBIVO®, TYZEKA®, LdT). A randomized, double-blind trial of LdT (telbivudine) versus lamivudine in adults with compensated chronic hepatitis B. Idenix pharmaceuticals.

[36] Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2001;34(6):1225-41.

[37] Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology. 2004;39(3):857-61.

[38] INTRON® A Interferon alfa-2b, recombinant for Injection. Schering Corporation. 2004;

[39] Tassopoulos NC, Volpes R, Pastore G, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B.Lamivudine Precore Mutant Study Group. Hepatology. 1999;29(3):889-96.

[40] Hadziyannis SJ, Vassilopoulos D. Immunopathogenesis of hepatitis B e antigen negative chronic hepatitis B infection. Antiviral.Res 2001;52(2):91-8.

[41] Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981;1(5):431-5.

[42] Poynard,T., Chutaputti,A., Hwang S, Lim S, Heathcote,J., and Kuan,Y. Sustained Off-Treatment Hbeag Response In Telbivudine And Lamivudine Treated Hbeag-Positive Patients From The Globe Study. 2007;

[43] GLOBE study NV-02B-007 - 52 week CSR. 2007; CONFIDENTIAL

[44] Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354(10):1011-20.

[45] Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9(26):1-iv

[46] Data on file. Novartis AG Pharma. 2007;

[47] Lai C, Gane E, Liaw Y, et al. A Comparison of Telbivudine and Lamivudine in Patients With Chronic Hepatitis B. Accepted for publication in NEJM. CONFIDENTIAL

[48] Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65-73.

[49] Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective

study. Am J Gastroenterol 2006;101(8):1797-803.

[50] Adefovir Dipivoxil and Peginterferon Alfa-2a for the treatment of chronic hepatitis B. National Institute for Health and Clinical Excellence. http://guidance.nice.org.uk/TA96/guidance/pdf/English.

[51] Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation http://guidance.nice.org.uk/page.aspx?o=268716. Health Technol Assess 2006;10(28):iii-xiv, 1.

[52] Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1995;122(9):664-75.

[53] Curtis L, Netten A. Unit cost of health and social care 2006. PSSRU, University of Kent 2006.

[54] British National Formulary BNF54, 2007.

[55] http://www.nice.org.uk/pdf/TAP_Methods.pdf. Accessed June 2007.