All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

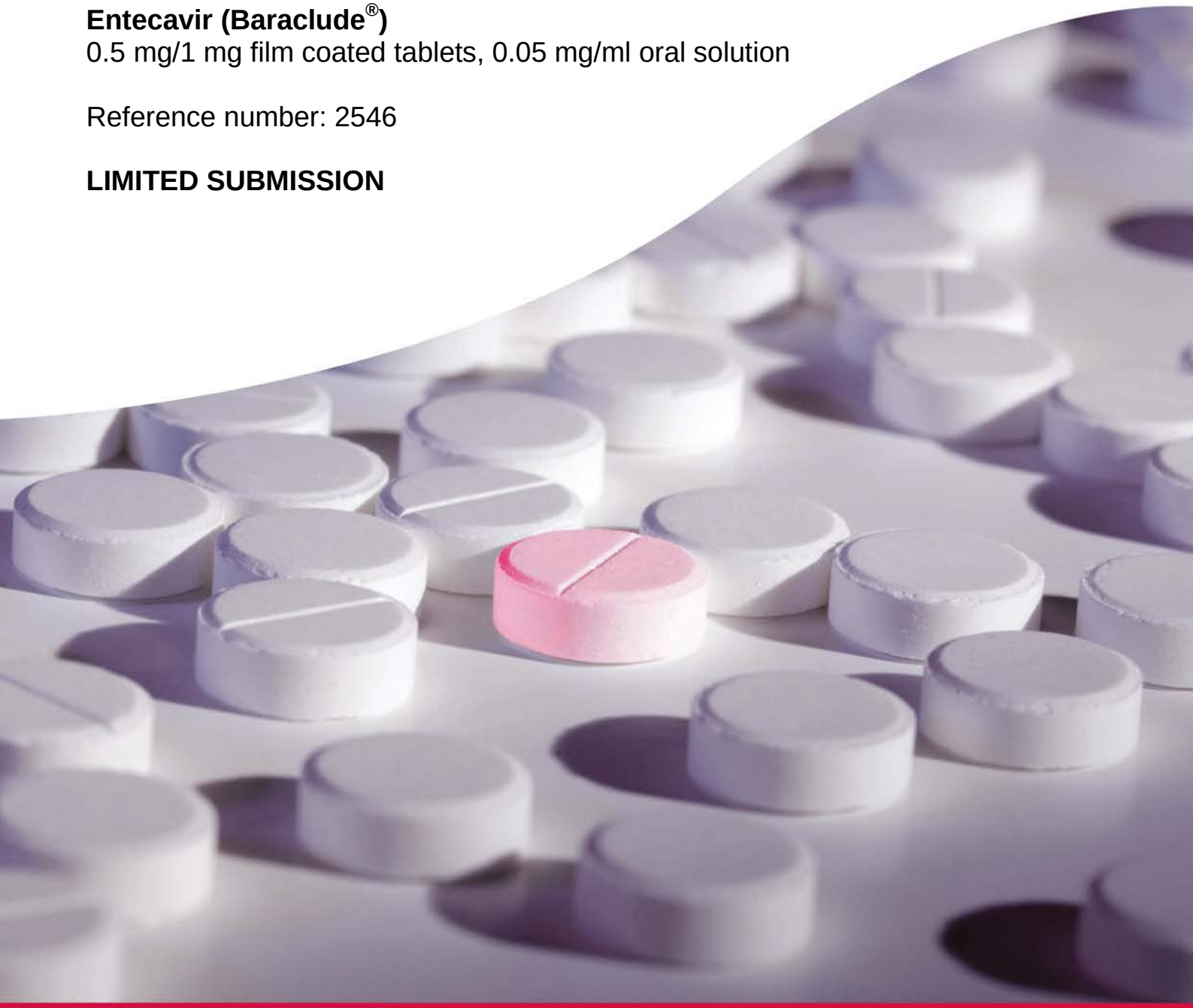
AWMSG SECRETARIAT ASSESSMENT REPORT

Entecavir (Baraclude®)

0.5 mg/1 mg film coated tablets, 0.05 mg/ml oral solution

Reference number: 2546

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Entecavir (Baraclude®)
0.5 mg/1 mg film coated tablets, 0.05 mg/ml oral solution

This assessment report is based on evidence from a limited submission by Bristol-Myers Squibb Pharmaceuticals Ltd on 28 November 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Entecavir (Baraclude®) for the treatment of chronic hepatitis B virus (HBV) infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum alanine aminotransferase (ALT) levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, refer to the Summary of product Characteristics (SPC)[2].
Dosing	Paediatric patients with body weight of at least 32.6 kg, should be administered a daily dose of one 0.5 mg tablet or 10 ml (0.5 mg) of the oral solution, with or without food. The oral solution should be used for patients with body weight less than 32.6 kg (refer to the dosing chart in the SPC for doses in these patients). The optimal duration of treatment is unknown, the SPC provides guidance on treatment discontinuation in accordance with current paediatric practice guidelines[2].
Marketing authorisation date	22 August 2014[3] (licensed for the treatment of chronic hepatitis B virus (HBV) infection in adults on 26 June 2006)[4].
Comparators	The comparator included in the company submission was tenofovir licensed for use in 12 to 18 year olds[1].
Limited submission details	Entecavir (Baraclude®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes two ongoing paediatric studies, a phase IIb dose-finding study (AI463028) and a phase III comparative efficacy study (AI463189). As there are no studies of entecavir versus an active comparator the company also refer to a placebo-controlled study of tenofovir in adolescents (age 12 to < 18 years)[5]. The company report that indirect comparison between studies was not possible due to the heterogeneity between populations, study duration, primary and secondary endpoints[1]. Therefore the tenofovir study will not be discussed.

2.1 Dose-finding Study (AI463028)

This was an open-label study assessing the pharmacokinetics, safety, tolerability and preliminary efficacy of entecavir in paediatric patients with chronic hepatitis B virus (HBV) infection. The primary objective of study AI463028 was to find a paediatric dosing regimen for entecavir to provide similar exposure to that seen in adults at the recommended dose[6]. A total of 24 nucleoside-naive and 19 lamivudine-experienced hepatitis B e antigen (HBeAg) positive patients with compensated liver disease aged 2 ≤ 18 were included in the study. In the nucleoside-naive patient group entecavir 0.015

mg/kg, up to a maximum dose of 0.5 mg once daily, achieved levels similar to those measured in adults given 0.5 mg once daily. Consequently this dose is used in study AI463189 in which all patients were nucleoside-naive[1].

2.2 Efficacy Study (AI463189)

This is an ongoing, randomised, double-blinded, placebo-controlled multicenter study; comparing the efficacy and safety of entecavir with placebo, in children with chronic hepatitis B (HB) who are HBeAg-positive, with compensated liver disease and elevated serum alanine aminotransferase (ALT)[7]. Patients (n=180) were randomised and stratified by age group (2 to ≤ 6 years; > 6 to ≤ 12 years; > 12 to < 18 years), 123 treated patients were included in the primary endpoint analysis (primary cohort). Randomised patients received entecavir 0.015 mg/kg up to 0.5 mg once daily (n=120) or placebo once daily (n=60) for up to 96 weeks. In the primary cohort 82 patients received entecavir and 41 patients received placebo[7].

The study was powered to demonstrate superiority of entecavir over placebo, the primary endpoint being the proportion of patients who achieved a combination of; HBV DNA < 50 IU/ml (~ 300 copies/ml) and HbeAg seroconversion at week 48 of the study. Key secondary endpoints were analysed at week 48 and included the proportion of patients with: HBV DNA < 50 IU/ml; ALT ≤ 1 x the upper limit of normal (ULN); HBV DNA < limit of quantitation (29 IU/ml); HBeAg seroconversion[7].

The proportion of patients who achieved the primary endpoint of HBV DNA suppression and HBeAg seroconversion at week 48 was higher in the entecavir group than in the placebo group (24.4% versus 2.4%; p=0.0049), superiority of entecavir against placebo was demonstrated[7]. The key secondary endpoints were supportive of this finding with the exception of HBeAg seroconversion which was 24.4% in the entecavir group and 12.2% in the placebo group (p=0.11) and therefore not statistically significant[6].

Results at 96 weeks were made available to the Committee for Medicinal Products for Human Use (CHMP), who ascertained that results were supportive of the 48 week analysis. The number of responders increased, particularly among those with high baseline HBV-DNA[6].

2.3 Safety

Pooled safety data from the two studies of entecavir in paediatric patients comprises a total of 173 nucleoside naive patients treated with entecavir for a median of 60 weeks[6]. No significant differences between entecavir and placebo were reported in terms of safety. Overall the incidence of adverse events (AEs) was higher in the lower age cohort although this seemed to be mainly due to the higher incidence of infections and respiratory AEs in the younger children[6]. No difference in growth (height or weight) was measured between entecavir and placebo groups at week 48 of study A1463189[7]. Overall the side effect profile of entecavir in children was not different from that observed in adults[6].

2.4 Points to note

- CHMP concluded that study AI463028 demonstrated comparative pharmacokinetics in paediatric patients as in adults. Subgroup analysis from study AI463189 showed that the proportion of responders was similar over the three age cohorts, which helps to confirm that the dosing regimen was appropriate[6].
- Study AI463189 demonstrated antiviral efficacy superior to placebo. CHMP note that the proportion of paediatric patients in the entecavir group with HB DNA < 50 IU/ml at week 48 (46%) was lower than in the pivotal HBeAg positive study in adults (67%). CHMP note that the reason for this difference is unclear[6].

The company suggest that the difference may be due, in part, to a lower degree of baseline immune activation in this paediatric population.

- A lower rate of virologic response (HBV DNA < 50 IU/ml) was observed in paediatric patients with baseline HBV DNA ≥ 8.0 $\log_{10}$ IU/ml. A caution has been added to the SPC to reflect this and states that entecavir should be used in these patients only if the potential benefit justifies the potential risk to the child (e.g. resistance). Since some patients may require long term or even life time management of chronic hepatitis B, consideration should be given to the impact of entecavir on future treatment options[2].
- In study A1463189 entecavir was less effective at reducing HBV DNA in paediatric patients with genotype D with 16% of these patients achieving HBV DNA < 50 IU/ml compared to other genotypes: A (73%); B (57%); C (65%) and other (50%). It was noted by CHMP that patients with genotype D tended to have higher baseline HBV DNA levels and the lower efficacy reported in this group is likely to be an effect of a small sample number and higher baseline viral loads[6].
- There is no information on the likely HB genotype demographic in Wales. In general genotypes A and D are dominant in Europe, B and C in Asia, and E in Africa[6,8]. However, genotypes will also depend upon the origins of local immigrant populations.
- In study AI463189 there was little difference in the safety profile of entecavir and placebo in the youngest age strata (2-6 years); however, CHMP note that with only 40 nucleoside naive patients in the pooled database for this age group there is a level of uncertainty. Any adverse effects on height and/or weight are unlikely to have been captured at the 48 week analysis in study AI463189. Follow up is planned at five years which would be expected to pick up any longer term adverse effects on growth[6].
- Entecavir for the indication under consideration is the only licensed treatment option for paediatric patients aged 2 ≤ 12 years with chronic hepatitis B[1]. Tenofovir is licensed for this indication in adolescents, aged 12 ≤ 18 years[9]. The company submission included a placebo-controlled study of tenofovir in adolescents (12 to < 18 years); however an indirect comparison was not possible due to the heterogeneity between populations, study duration and primary and secondary endpoints.
- The National Institute for Health and Care Excellence (NICE) guidance TA153 approves use of entecavir as an option for the treatment of adults with chronic hepatitis B[10].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company have estimated that approximately 35 paediatric patients (aged 0 to 18 years) would be eligible for treatment in Wales. This figure is derived from data presented by the Public Health Laboratory Service, based on surveillance from 1988–2000[1,11,12].

The company have calculated the annual cost of treatment for 35 patients to be £155,000 (0.5 mg tablets) or £257,812 (50 microgram/ml oral solution)[1].

Tenofovir is licensed for use in 12 ≤ 18 year olds and the company have estimated that of the 35 patients seven would fall into this age group, four of whom may be treated with entecavir instead of tenofovir[1]. The annual treatment cost of tenofovir is £2925.60 per patient[13]. The company estimate the annual treatment cost of entecavir as £7366.05 per patient (based on the maximum dose of the oral solution). The company state that the total cost of treating 28 patients aged 0 ≤ 11 and 4 patients aged 12-18 years with entecavir would be approximately £235,714[1].

3.1.1 AWTTC critique

- The estimate of 35 patients eligible for treatment in Wales is based on laboratory surveillance figures from 1988-2000, data which may not reflect current figures[11,12]. The figure is derived from the cumulative total of recorded infections in 2–18 year olds in England and Wales per 100,000, the All Wales Therapeutics and Toxicology Centre (AWTTC) are unable to verify how this figure has been adjusted for the Welsh population.
- There is no estimation given as to how many paediatric patients with confirmed chronic hepatitis B infection would need treatment according to current clinical practice guidelines (within the licensed indication) for treatment with entecavir[14].
- The total annual cost estimate assumes that all eligible patients will receive the oral solution; this may therefore be an overestimation as it would be expected that patients aged 12-18 years would be prescribed the tablet formulation.

3.2 Comparative unit costs

The unit costs for entecavir and tenofovir are shown in Table 1.

Table 1. Examples of costs for entecavir (Baraclude®) and tenofovir (Viread®) for treatment of chronic hepatitis B in paediatric patients

Medicine	Example dose	Approximate annual cost*
Entecavir (Baraclude®) film-coated tablets 0.5 mg	Over 32.6 kg 0.5 mg od	£4419.66
Entecavir (Baraclude®) oral solution 50 micrograms/ml	In patients less than 32.6 kg the once daily recommended dose range is from: 10.0–14.1 kg 4.0 ml thereafter in 0.5 ml increments up to ≥32.6 kg 10.0 ml	£2946.42 (4.0 ml od) to £7366.05 (10.0 ml od)
Tenofovir (Viread®) film-coated tablets 245 mg	Adolescents 12 to <18 years 245 mg od	£2925.60
Tenofovir (Viread®) oral granules 33 mg/g	Adolescents 12 to <18 years 245 mg (7.5 scoops) od	£2486.56
od: once daily *BNF list price[13] This table does not imply therapeutic equivalence of medicines or the stated doses. See relevant SPCs for full dosing details[2,9,15].		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, entecavir (Baraclude®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that entecavir (Baraclude®) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 05 December 2014
Date range of evidence search: No date limits were applied to database searches.

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Appendix: Previous AWMSG secretariat assessment report (published January 2012)

In January 2012, AWMSG appraised entecavir (Baraclude®) for the treatment of chronic hepatitis B virus infection in adults with decompensated liver disease (AWTTC reference number 438). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of entecavir (Baraclude®) for the treatment of chronic hepatitis B virus infection in:

- adults with decompensated liver disease; and
- nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum alanine aminotransferase (ALT) levels, or histological evidence of moderate to severe inflammation and/or fibrosis (AWTTC reference number 2546).

The original report for AWTTC reference number 438 is included below for completeness.

AWMSG Secretariat Assessment Report – Advice no. 0212
Entecavir (Baraclude®▼) 0.5 mg and 1 mg film-coated tablets and 0.05 mg/ml oral solution

This assessment report is based on evidence submitted by Bristol-Myers Squibb Pharmaceuticals Ltd on 5 September 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Entecavir (Baraclude®▼) is indicated for the treatment of chronic hepatitis B virus infection in adults[1]. This submission covers the licence extension for treatment of chronic hepatitis B patients with decompensated liver disease[1].
Dosing	The recommended dose for patients with decompensated liver disease is 1 mg once daily. Please see Summary of Product Characteristics (SPC) for dosing in lamivudine-refractory patients and patients with creatinine clearance < 50 ml/min[1].
Marketing authorisation date	28 February 2011[2,3] (licensed for compensated liver disease on 26 June 2006[1]).

2.0 DECISION CONTEXT

2.1 Background

Chronic hepatitis B (CHB) is defined as hepatic inflammation with persistence (> 6 months) of the hepatitis B surface antigen (HBsAg) following acute infection with the hepatitis B virus (HBV)[4–7]. The Department of Health estimated the UK prevalence of CHB infection to be 0.3% (180,000 people) in 2002[8], and, based on 1995–2000 data, the Health Protection Agency reported an estimated 269 new chronic infections per year in England and Wales[9].

Patients with chronic infection are at risk of developing serious hepatic complications[4,10–12]. Progression of the disease may lead to a 'decompensated' state, wherein liver damage occurs to such an extent that liver function is lost, resulting in severe clinical events including ascites, internal bleeding and hepatic encephalopathy[11]. The applicant company estimate that there are 15 patients who have CHB with decompensated liver disease in Wales[3].

Hepatitis B early antigen (HBeAg) may be used as an indicator of HBV replication (see Glossary for further information), although there are variants of the virus that do not express this antigen. Patients are described as HBeAg-positive or HBeAg-negative according to HBeAg secretion[13]. For HBeAg-positive patients, the progression of CHB is associated with a transition from an active to an inactive state following seroconversion, i.e. the development of anti-HBe antibodies. This results in low or undetectable serum HBV DNA levels, which confers a good quality of life and low risk of liver decompensation[14].

Patients that are HBeAg-negative (which may follow seroconversion) experience periodic reactivation and fluctuations in HBV DNA levels, resulting from the harbouring of HBV variants with nucleotide substitutions. This group of patients are at high risk of developing decompensated liver disease. The HBeAg-negative form of the disease represents the majority of cases in many areas, including Europe. The five-year cumulative incidence of progression to a decompensated state is approximately 20%, and patients with decompensated cirrhosis have a 14–35% probability of survival at five years[14].

Patients with decompensated liver disease should begin anti-retroviral therapy as a matter of urgency, with the aim of inhibiting HBV replication and increasing the chance of seroconversion[14]. Treatment for patients at a decompensated stage has been shown to improve liver function (potentially returning to a compensated state) and decrease mortality[15]. Anti-retroviral treatment may also be used to delay or to prevent the need for transplantation and to reduce the risk of HBV recurrence on the graft[11]. Interferon-alpha is commonly used for treatment of CHB but is contraindicated in patients with decompensated liver disease[14]. Instead, nucleoside/nucleotide analogues, which act by inhibiting the reverse transcriptase responsible for HBV replication, are recommended[14]. Entecavir (ETV) is a guanosine nucleoside analogue that functionally inhibits HBV polymerase and therefore HBV DNA synthesis[1].

2.2 Comparators

In addition to ETV, nucleoside/nucleotide analogues currently licensed for treatment of CHB patients with decompensated liver disease are:

- Tenofovir disoproxil fumarate (TDF, Viread®▼)
- Adefovir dipivoxil (ADV, Hepsera®)
- Lamivudine (LVD, Zeffix®) in combination with another antiviral drug without cross-resistance to LVD

The Welsh Medicines Partnership (WMP) requested ADV, LVD and TDF as comparators to ETV. LVD is not licensed as a monotherapy for CHB patients with decompensated disease; therefore, in agreement with WMP, the company provided information for ADV and TDF as comparators, but did not believe that there was a sufficient evidence-base to allow a meaningful comparison against TDF to be made in this patient population (see Section 3.4).

2.3 Guidance and related advice

- European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B. 2009[14]. These guidelines recommend ETV or TDF as first-line monotherapies for CHB patients. This extends to patients with decompensated liver disease; however, the guidelines note the lack of safety data for these agents in this population[14].
- NICE technology appraisal guidance 153: Entecavir for the treatment of chronic hepatitis B. 2008[16]. This guidance document recommends ETV as an option for the treatment of CHB with compensated liver disease[16].
- All Wales Medicines Strategy Group (AWMSG). Tenofovir disoproxil fumarate (Viread®▼) is recommended as an option for use within NHS Wales for the treatment of CHB in adults with decompensated liver disease. 2011[17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission assessed ETV in CHB patients with decompensated liver disease, and included details of one phase III trial which compared ETV and ADV (AI463048)[18], which they consider pivotal; one phase II safety trial which compared TDF, ETV and emtricitabine (FTC)/TDF in combination[15]; and an uncontrolled, non-randomised, single-centre study of ETV monotherapy[19]. Patients enrolled in the single-centre study received 0.5 mg ETV (a 1 mg dose is recommended by the SPC) and were compared with CHB patients with compensated liver disease; therefore, this study is of limited relevance and will not be discussed further[3].

3.1 Phase III trial (AI463048)

AI463048 was a randomised, multicentre, open-label phase III trial which compared the safety and efficacy of ETV and ADV in CHB patients with hepatic decompensation, defined by a Child–Turcotte–Pugh (CTP) score of ≥ 7 (see Glossary for further information)[18]. Patients co-infected with hepatitis C virus, hepatitis D virus or human immunodeficiency virus were excluded. Included patients were HBeAg-positive or -negative, and were HBV nucleoside-naive or LVD-experienced. Study participants (n = 195, aged ≥ 16 years) were randomised 1:1 to receive 1 mg ETV (n = 101) or 10 mg ADV (n = 94) daily. Groups were balanced in terms of prior LVD treatment and HBeAg status.[18].

The primary endpoint was the mean change in HBV DNA level from baseline at week 24[18]. The mean change in HBV DNA level from baseline was also measured at week 48 as a secondary endpoint, in addition to the proportion of patients with HBV DNA < 300 copies/ml and changes in CTP and model for end-stage liver disease (MELD) scores at weeks 24 and 48 (see Glossary for further information). HBeAg loss or seroconversion, HBsAg loss, and HBV resistance were also monitored. The company submission included 96-week data for these endpoints which remains confidential. Of the 195 patients randomised, 191 were treated, with non-completers regarded as failures. The mean change from baseline for the primary endpoint was significantly greater in patients treated with ETV than ADV at week 24 (-4.48 $\log_{10}$ copies/ml versus -3.40 $\log_{10}$ copies/ml; $p < 0.0001$). The proportion of subjects achieving HBV DNA < 300 copies/ml was greater with ETV than ADV at week 24 (49% versus 16%, respectively; $p < 0.0001$), and week 48 (57% versus 20%, respectively; $p < 0.0001$)[3]. These results were supported by the subgroup analysis of LVD-resistant patients. Improvements in CTP and MELD scores at week 48 were comparable between the study arms: 35/100 (35%) ETV-treated patients and 25/91 (27%) ADV-treated patients had a ≥ 2-point reduction in CTP score, while the mean change in MELD score was -2.6 and -1.7 for the ETV and ADV arms respectively[18].HBeAg loss and seroconversion were higher in patients treated with ADV than ETV at week 24[3]. HBsAg loss was observed in five patients treated with ETV, but no patients treated with ADV at week 48[18]. Up to week 48, no patients showed resistance to the study drug; however, beyond this, three ETV patients (all LVD-refractory at baseline) and six ADV patients (two LVD-refractory at baseline) showed resistance to the study drug[18].

3.2 Phase II trial

The company submission included a phase II, double-blind, multicentre, randomised study that compared TDF alone, FTC/TDF in combination and ETV alone for CHB patients with decompensated liver disease and a CTP score of 7–12[15]. Patients (n = 112, aged 18–69 years) were switched from their current therapy and randomised 2:2:1 to each treatment arm (45 TDF [300 mg], 45 FTC/TDF [200/300 mg] and 22 ETV [0.5 mg or 1 mg]). The primary endpoints of this study were related to safety.

Efficacy parameters were measured as secondary endpoints, but were not statistically powered (see Section 3.4). These included HBV DNA level, HBeAg/HBsAg loss and seroconversion, and CTP and MELD scores.

Results at week 48 showed undetectable HBV DNA levels (< 400 copies/ml) in 70.5% and 72.7% of patients in the TDF and ETV treatment arms, respectively. No patients receiving ETV presented HBeAg loss or seroconversion. Three patients receiving TDF achieved HBeAg loss. In addition, 25.9% and 41.7% of patients in the TDF and ETV treatment arms, respectively, had a ≥ 2 point decrease in CTP score[15].

3.3 Comparative safety

The frequency of adverse events (AEs) and serious AEs (SAEs) in study AI463048 was comparable between ETV and ADV treatment groups[18]. Ten (11%) ETV-treated patients required dose reduction due to a change in renal function, compared with one (1%) patient receiving ADV. Lactic acidosis occurred in one patient (1%) in the ETV arm, but resolved without dose interruption. Seven (7%) patients treated with ETV and five (6%) patients treated with ADV discontinued therapy due to AEs. The cumulative rates of hepatocellular carcinoma (HCC) were 12/202 (12%) for ETV and 18/89 (20%) for ADV[18].

The co-primary endpoints of the phase II study were safety-related: tolerability failure (permanent discontinuation due to a treatment-related AE) and confirmed serum creatinine increase ≥ 0.5 mg/dl or confirmed serum phosphorous < 2.0 mg/dl[15]. Tolerability failure occurred in 4-10% of patients and was comparable between treatment groups. Four TDF patients and one ETV patient had a confirmed change from baseline in serum creatinine of ≥ 0.5 mg/dl or phosphorous < 2.0 mg/dl (p = 1.000). There were no statistically significant differences between the combined data for TDF and FTC/TDF arms, compared with the ETV group, for any renal parameter. Most AEs occurring in ≥ 5% of patients were comparable across treatment arms and were consistent with decompensated liver disease. A total of 11 (24.4%), 19 (42.2%) and 5 (22.7%) SAEs occurred in the TDF, FTC/TDF and ETV treatment arms, respectively, with the most common SAEs reported to be gastrointestinal disorders, infections and infestations, and hepatobiliary disorders[15,20].

3.4 WMP critique

- A considerable problem with long-term nucleoside/nucleotide analogue treatment is the emergence of resistance. Resistance to LVD has been shown to occur in 70–80% of patients without HBeAg seroconversion after four years of treatment[21]. Therefore, LVD is no longer recommended as monotherapy[14,22]. Add-on therapy with ADV has been used historically; however, ADV also has a low genetic barrier to resistance[20] and its use may be limited by nephrotoxicity[11]. The Committee for Medicinal Products for Human Use (CHMP) states that, recently, the treatment of CHB almost exclusively relies on TDF and ETV, which are widely acknowledged as being the gold standards, due to their potent antiviral activity and high genetic barrier to resistance[23]. Further, EASL guidelines recommend ETV or TDF for decompensated liver disease[14]. ETV has been shown to be less efficacious in LVD-refractory patients and prior use of LVD infers an increased risk of resistance to ETV[15,24]. As a result, the SPC for ETV states that in patients with both decompensated liver disease and LVD-resistant HBV, combination use of ETV plus a second antiviral agent (which does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy[1]. No data for the use of ETV in combination with such an agent has been provided in the company submission. The EASL guidelines recommend adding TDF where LVD resistance is observed[14].

- CHMP state that in terms of improvement of hepatic function, no definite advantage of ETV over ADV was observed during study AI463048[23].
- The CTP score is a useful measure for patients with decompensated liver disease as it incorporates two clinical variables that relate to features of decompensation (the presence of ascites and hepatic encephalopathy). Decompensated disease is generally accepted to be classified as a CTP score of 7–15[18,25]. Study AI463048 included patients with a CTP score of ≥ 7, and had a mean baseline CTP score of 8.59 (balanced between treatment groups)[18]; whereas the phase II trial described excluded patients with very advanced disease (for example those with CTP score > 12, variceal bleeding and grade 3–4 hepatic encephalopathy) and had a median CTP score of 7 in each treatment arm[15].
- Of the 22 patients treated with ETV in the phase II trial, thirteen received less than the recommended 1 mg dose[15].
- Of 191 patients included in AI463048, 104 (54%) were Asian and 63 (33%) were white[18]. Additionally, in the phase II trial, of 112 patients, 60 (54%) were Asian and 47 (42%) were white. This would not appear to be representative of the population of Wales. However, the company highlight that up to 96% of all new CHB cases in England and Wales are migrants from areas of intermediate or high prevalence of CHB infection, which include North America, parts of South America, sub-Saharan Africa and most of Asia[3,26].
- No quality-of-life data are provided.

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a primary cost-effectiveness analysis (CEA) measuring cost per life-year gained and cost per HCC-free life-year gained for ETV compared with ADV in CHB patients with decompensated liver disease[3]. A supplementary cost-utility analysis (CUA) measuring the cost per quality-adjusted life-year (QALY) gained has also been provided, but the company considers that the CEA is more informative due to the inconsistencies in the available utility weight data. The model reflects monotherapy use, and as such appears to relate only to the use of ETV in patients who have no known resistance to LVD. A comparison of ETV against TDF has not been made as the company feels there is insufficient data available to conduct a meaningful analysis.

The analysis is based on a Markov model in which patients with decompensated disease can remain in that state, move to a HCC state, receive a liver transplant and proceed to post-liver transplant health state, or die. Regression from decompensated disease to compensated disease is not permitted. The probabilities of transitions between different health states are derived from a direct clinical comparison of ETV and ADV in the study of CHB in adults with decompensated liver disease (trial AI463048)[18], and US Liver Transplant Registry data. See Appendix 1 for further details.

4.1.2. Results.

The results of the base case analyses are summarised in Table 1.

Table 1. Company-reported results of cost-effectiveness of ETV versus ADV in the treatment of CHB in adults with decompensated liver disease.

Base case	ETV	ADV	Difference
Primary CEA			
Drug costs	£6,618	£4,768	£1,851
Total costs	£31,272	£28,880	£2,392
Total life years gained	2.24	2.17	0.07
ICER (cost per life-year gained)	**£35,079**		
HCC-free life years gained	2.09	2.00	0.09
ICER (cost per HCC-free life-year gained)	**£27,540**		
Supplementary CUA			
Total QALY gains	1.44	1.18	0.26
ICER (cost per QALY gained)	**£9,291**		

ADV = adefovir dipivoxil; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ETV = entecavir; ICER = incremental cost-effectiveness ratio; HCC = hepatocellular carcinoma; QALY = quality-adjusted life-year

One-way sensitivity analyses were performed to explore the impact of uncertainty in model parameters, including transition probabilities between different health states, time horizon, discount rate, and costs associated with the treatment of different health states. The model was most sensitive to the assumed time horizon, with the incremental cost per life-year gained decreasing to £28,574 using a five-year time horizon. The model was relatively insensitive to variation in the discount rate (0–6%), and to 25% variation in transition probabilities between different health states and costs associated with these health states. However, the CUA model of ETV versus ADV was sensitive to the utility estimates, with the incremental cost-effectiveness ratio (ICER) increasing to £29,646 per QALY gained under the worst-case scenario explored for estimating utilities. No multi-way or probabilistic sensitivity analyses were presented by the company.

4.1.3 WMP critique

Strengths of the economic evidence include:

- Efficacy data used in the economic model were derived from a direct comparative study of ETV and ADV in patients with CHB and decompensated liver disease.

Limitations of the economic evidence include:

- The model compares ETV monotherapy against ADV monotherapy, which is likely to be appropriate only in patients with no known LVD resistance. Efficacy data are derived from study AI463048, in which around 35% of patients had evidence of LVD resistance at baseline.
- The economic evidence is limited to a comparison of ETV against ADV. Due to a lack of comparison against TDF, the economic evidence would seem incomplete.
- The economic evidence presented by the company assumes that patients will receive ETV as tablets only. There is a significant difference in acquisition costs between the tablet and oral solution formulations (£12.11 per mg versus £40.36 per mg, respectively), which is not considered.

- The company has highlighted the uncertainty associated with utility weight estimates available in the literature to inform its CUA. The approach adopted by the company to generate utility weights appears to compound that uncertainty and is potentially biased. Collectively, it is uncertain how reliable and informative the resultant CUA is.
- Sensitivity analyses are limited to one-way analyses, and there is no exploration of combined uncertainty across multiple parameters.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches identified one published study comparing the cost-effectiveness of ETV compared to ADV in the treatment of CHB in adults with compensated and decompensated liver disease[27]. The CUA was based on a Markov model, including six health states: "chronic HBV cirrhosis", "compensated cirrhosis", "decompensated cirrhosis", "HCC", "liver transplant" and "death". In contrast to the model provided to AWMSG, the published model assumed a one-year model cycle and a lifetime horizon. Patients with decompensated disease could regress to compensated disease and the range of utility values differs from those used in the current model. However, the model assumed that patients received 0.5 mg ETV once daily, rather than 1 mg as recommended in the UK for decompensated disease, and available efficacy data were more limited at the time of the published analysis. The ICER for ETV therapy versus ADV was $25,626 per QALY gained, assuming 50% of the modelled cohort had decompensated disease at baseline. Changing the proportion of patients with decompensated disease is reported to have produced 'qualitatively similar' results, but details are lacking[27]. Given the differences in the modelled pathway, the assumed ETV dose, and the health care setting, the applicability of this study to current practice in Wales is unclear; however it does highlight different approaches to modelling the current decision problem.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on UK prescription data for 2008 and company data on file, the company estimates that there are currently 15 patients with chronic HBV infection and decompensated liver disease in Wales[3]. In the absence of incidence data, the company assumes this figure to remain static, with new cases balanced out by deaths. The company assumes that all patients will receive antiviral therapy. Assuming an increase in market uptake for ETV from 15%, in year 1 to 26% in year 5, the total number of patients treated with ETV is expected to increase from 2 to 4 over a five-year period. It is assumed that TDF uptake would be the same as ETV uptake over the same period. Net treatment costs are derived on the assumption that one-third of patients who would be eligible for ETV would instead receive TDF, and two-thirds would instead receive ADF. The estimated numbers of patients and the company-reported costs over a five-year period are shown in Table 2.

Table 2. Company-reported costs associated with ETV treatment of adult patients with CHB and decompensated liver disease.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	15	15	15	15	15
Uptake	15%	17%	20%	23%	26%
Number of treated patients	2	3	3	3	4
Net treatment costs	£1,957	£2,936	£2,936	£2,936	£3,915
Administration and monitoring	-£63	-£74	-£74	-£74	-£84
Overall net costs	£1,895	£2,862	£2,862	£2,862	£3,830

Three scenario analyses were conducted to address the uncertainty associated with the number of patients eligible for treatment with ETV and the variation in market uptake for ETV. When the number of patients eligible for ETV treatment was doubled, the overall net cost of treatment in year 1 was estimated as £4,757 rising to £7,619 in year 5. As expected, a doubling of the market share for ETV produced the same changes in costs and a decrease in market uptake by 50% reduced overall treatment costs to £968 in year 1 and £1,895 in year 5.

5.1.2 WMP critique

The company appears to have made reasonable efforts to estimate the number of patients eligible for ETV treatment in Wales, although it is not possible to verify their data on file. However, the assumed savings associated with administration and monitoring costs for ETV are subject to uncertainty. Patients with decompensated liver disease will require routine monitoring irrespective of the antiviral treatment they receive, and it is not clear how actual resources will differ in practice. ETV is available as tablets and oral solution, which differ significantly in acquisition costs (£12.11 per mg versus £40.36 per mg, respectively). The company's estimates are based only on the costs of the tablet formulation.

5.2 Comparative unit costs

Table 3 includes acquisition costs for individual agents indicated for use for the treatment of CHB in adults with decompensated liver disease. It should be noted that combination therapy, rather than monotherapy, may be required depending on individual patients' treatment histories and resistance profiles. The relevant SPC should be consulted for full dosing details.

Table 3. Examples of drug acquisition costs for the treatment of CHB in adults with decompensated liver disease.

	Regimen	Cost per year
ETV (Baraclude®▼) 0.5 mg and 1.0 mg tablets	1 mg once daily	£4,419.66
ETV (Baraclude®▼) 0.05 mg/ml oral solution	1 mg once daily	£15,468.70
ADV (Hepsera®) 10 mg tablets	10 mg once daily	£3,610.22
TDF (Viread®▼) 245 mg tablets	245 mg once a day	£2,925.60
ADV = adefovir dipivoxil; ETV = entecavir; TDF = tenofovir disoproxil fumarate *Costs are based on MIMS list prices as of 14 Oct 2011[28].* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that ETV is not suitable for shared care within NHS Wales.

6.2 Ongoing studies

The company submission did not provide details for any ongoing studies.

GLOSSARY

Child–Turcotte–Pugh (CTP) score

This method of scoring is used to assess the severity of a hepatic condition and predict a patient's prognosis[29,30]. The following five variables are considered:

- Total bilirubin
- Serum albumin
- International normalised ratio (INR)
- Ascites
- Hepatic encephalopathy

A score of between one and three (three being most severe) is assigned to each of these factors. The sum of the scores provides the CTP score, which corresponds to a grade of A, B or C. This grade is used as a general means to predict the prognosis of the patient (Table 1)[31,32].

Table 1. CTP scoring and associated outcome predictions.

Points	Class	One-year survival	Five-year survival
< 7 (well-compensated disease)	A	84%	44%
7–9 (significant functional compromise)	B	62%	20%
> 9 (advanced decompensated disease)	C	42%	21%

Hepatitis B early antigen (HBeAg)

HBeAg is a secretory protein of the hepatitis B virus[33]. The presence of HBeAg in a host's serum is typically associated with very high rates of viral replication and enhanced infectivity[14]. During the course of HBV infection the HBeAg may be cleared and antibodies to the 'e' antigen (anti-HBe) will arise. This 'seroconversion' is usually associated with a dramatic decline in viral replication. Some variants of the hepatitis B virus, however, do not produce the 'e' antigen[14].

Model for end-stage liver disease (MELD) score

This scoring method is used to assess the severity of chronic liver disease and to predict a patient's prognosis[34]. The variables considered are:

- Serum bilirubin
- Serum creatinine
- INR

The following formula is then applied to calculate the MELD score:

MELD = 3.8x loge (bilirubin [mg/dl]) + 11.2 x loge (INR) + 9.6 x loge (creatinine [mg/dl]) + 6.4

The result is interpreted as in Table 2[34].

Table 2. MELD scoring and associated outcome predictions.

Score	Three-month mortality
≥ 40	100%
30–39	66%
20–29	56%
10–19	26%
< 9	8%

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Appendix 1. Additional Health Economic Analysis Information

Table 1. Health economic analysis detail[3]

	Base case model	Appropriate?
Comparator(s)	ETV 1.0 mg once daily versus ADV 10 mg once daily.	Yes. WMP originally requested comparison against ADV and LVD, but the company has justified the lack of comparison against LVD on the basis of its inferior genetic barrier to development of resistance, which would probably preclude its widespread use in the target patient population. The model only compares ETV monotherapy against ADV monotherapy. The SPC for ETV notes that in patients with both decompensated liver disease and LVD-resistant HBV, combination use of ETV plus a second antiviral agent (which does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy[1]. The modelled costs, therefore, seem to relate only to the use of ETV in patients who have no known resistance to LVD. TDF is also licensed for use in patients with CHB and decompensated liver disease. The company notes that TDF is not currently recommended specifically for use in Wales at the time of the ETV submission, and that the trial of tenofovir in patients with decompensated liver disease is unsuitable as a source of data for comparison with entecavir. The company therefore precludes tenofovir as a relevant comparator in the economic model. However, the economic evidence in support of ETV would seem incomplete in the absence of a comparison against TDF (and it is of note that the company has considered TDF as a comparator in its budget impact analysis).
Population	Adults with CHB and decompensated liver disease.	Yes, in line with the licensed indication. However, the company makes little reference to the potential for development of resistance with ETV monotherapy in patients who have demonstrated LVD resistance. Based on the ETV SPC[1] and EPAR[2], which recommend the use of ETV combination therapy rather than monotherapy in patients with decompensated disease and evidence of LVD resistance, the modelled population seems to reflect the use of ETV in patients with no known resistance to LVD.

Table 1. Continued

	Base case model	Appropriate?
Analysis type	Base-case CEAs of ETV versus ADV, generating cost per life-year gained and cost per HCC-free life-year gained estimates have been provided. Supplementary CUAs have also been provided by the company in response to a request from WMP. A Markov model has been developed in which patients with decompensated disease who are HCC-free may progress to liver transplant (in the first year only), HCC or death. Patients with HCC may only undergo liver transplant in the first three months. Regression to compensated disease is not permitted. Salvage therapy with TDF is not considered	CUA is the preferred type of analysis. The company argues that the available utility data are inadequate to provide reliable estimates of incremental costs per QALY gained. However, an attempt has been made to provide supplementary CUAs, using a theoretical model to estimate relevant utility weights for decompensated disease states. Patients enrolled in trial AI463048, which provided the comparative efficacy data, were ETV, ADV and TDF treatment-naive. The model does not consider the use of second-line or salvage therapy with TDF.
Perspective	NHS Wales.	Yes, the analysis considered direct medical costs only.
Time horizon	The base case analysis assumes a three-year time horizon. Sensitivity analysis considers one and five year time horizon.	A lifetime analytical time horizon would be appropriate. The model is sensitive to changes in time horizon, with the incremental cost per life-year gained decreasing to £28,574 using a five-year time horizon.
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes. Sensitivity analysis considers 0% and 6% discount rates.	Yes.
Efficacy	Overall survival and HCC-free survival data for ETV and ADV were derived from trial AI463048[18]. The observed data were reportedly fitted with sequential Weibull curves to estimate survival rates. The rate of liver transplantation and survival post-transplant appears to be taken from US registry data.	Yes. Efficacy data used in the economic model were derived from direct comparative data for ETV and ADV from trial AI463048. Around 35% of patients enrolled in that trial had evidence of LVD resistance at baseline[18], and in such patients combination use of ETV plus a second antiviral agent (which does not share cross-resistance with either LVD or ETV) should be considered in preference to ETV monotherapy[1]. The US registry data providing rates of liver transplantation and survival post-transplant have not been verified by WMP, and appear to relate to registrations dating back to 1999. It is unclear if these reflect likely transplant rates and outcomes in UK practice today, although exploration of rates in the range +/-25% appears to have little impact on the estimated incremental cost per life-year gained.
Adverse events	Adverse events were considered to be the same for ETV and ADV; therefore, adverse events were not incorporated into the model.	Yes. However, 11% of patients treated with ETV (compared to 1% treated with ADV) in study AI463048 required dose reduction due to a change in renal function.

Table 1. Continued

	Base case model	Appropriate?
Utility values	Utility values were not collected in trial AI46304 and were not used in the base case CEA. Utility values for the supplementary analyses provided by the company have been derived from the published literature relating to hepatitis B and C. A theoretical model has been developed in which it is assumed that utility of patients with decompensated cirrhosis decreases over time, with the rate of this decrease being dependent on response to treatment (patients with serum HBV DNA < 300 copies/ml).	The company highlights that robust utility values for the modelled health states are lacking. Several estimates of utility values in patients with hepatitis B and C were identified in the literature and appear to vary substantially for decompensated disease (0.35 to 0.72). The company has developed a model under the assumption that the utility weight for decompensated disease state would decrease in the range 0.72 to 0.35 over time. A key assumption in this model is that the response rate for ETV and ADV patients at 12 months (57% and 20% respectively) is maintained to 39 months. The resultant utility values used in the base case supplementary CUA are therefore biased in favour of ETV, and sensitivity analyses indicate the model is sensitive to the utility values that are assumed. The source of utility values for patients with HCC and liver transplant are not specified and their impact is not explored in sensitivity analyses.
Resource use and costs	Costs incorporated in the economic model included the acquisition costs of ETV (as tablets) and ADV, and costs associated with different health states (decompensated cirrhosis, HCC, liver transplant and post liver transplant and death). It was assumed that there are no differences in the utilisation of other healthcare services/resources between patients receiving ETV and ADV. Costs of treating adverse events were not included in economic analysis as they were assumed to be the same for ETV and ADV.	Yes. Costs for treatment of decompensated cirrhosis were taken from HTA report (2006)[35] and inflated to 2010. There is a large difference in the costs of the tablet and the oral solution formulations of ETV (£12.11 per mg versus £40.36 per mg, respectively). Only the cost of the tablet formulation is considered in the economic model.
Uncertainty and scenario analyses	One-way sensitivity analyses were conducted for time horizon (one and five years), discount rate (0%-6%), utilities for HCC-free health state (0.35 and 0.72), costs associated with different health states (25% variation) and transition probabilities between different health states (25% variation). The supplementary analyses also include sensitivity analyses in relation to utility estimates.	Sensitivity analyses presented in the company submission are limited. No multi-way or probabilistic sensitivity analyses have been reported.
Model provided?	Yes.	Yes.

ADV = adefovir dipivoxil; CEA = cost-effectiveness analysis; CHB = chronic hepatitis B; CUA = cost utility analysis; ETV = entecavir; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; LVD = lamivudine; QALY = quality-adjusted life-year; SPC = Summary of Product Characteristics; TDF = tenofovir disoproxil fumarate; WMP = Welsh Medicines Partnership.