AWMSG Secretariat Assessment Report – Advice no. 1411
Tenofovir disoproxil fumarate (Viread®▼) for the treatment of chronic hepatitis B in adults with decompensated liver disease

This assessment report is based on evidence submitted by Gilead Sciences Ltd on 8 April 2011.

1.0 PRODUCT DETAIL

Licensed indication under consideration	Tenofovir disoproxil fumarate (Viread®▼) is indicated for the treatment of chronic hepatitis B (CHB) in adults. This submission covers the licence extension for CHB patients with decompensated liver disease[1]. Please refer to the Summary of Product Characteristics (SPC) for licensed indications not covered in this submission[1].
Dosing	The recommended dose for the treatment of CHB is 245 mg (one tablet) once daily taken orally with food. Therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of CHB. The optimal duration of treatment is unknown[1]. Each tablet contains 245 mg of tenofovir disoproxil (as fumarate), equivalent to 300 mg of tenofovir disoproxil fumarate, or 136 mg of tenofovir[1].
Marketing authorisation date	6 September 2010[2] (licensed 23 April 2008 for the treatment of CHB in adults with compensated liver disease[1,3]).

2.0 DECISION CONTEXT

2.1 Background

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)[5–8]. In 2002, the Department of Health estimated the UK prevalence of CHB infection to be 0.3% (180,000 people)[9]. In addition, the Health Protection Agency reported an estimated 269 new chronic infections per year in England and Wales based on 1995–2000 data[10]. The applicant company estimate that there are up to 25 patients who have CHB with decompensated liver function in Wales, and the number eligible for treatment is in the range of 8 to15[4].

Patients with chronic infection are at risk of developing serious hepatic complications including cirrhosis and hepatocellular carcinoma[5,11–13]. Further progression may lead to a 'decompensated' state where liver function is lost, resulting in severe clinical complications such as ascites, jaundice, internal bleeding and hepatic encephalopathy[12]. Hepatitis B early antigen (HBeAg) is an indicator of HBV replication (see Glossary for further information), although there are variants of the virus that do not express this antigen. Patients with CHB may be either HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted[14]. 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[15]. 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 are at high risk of developing decompensated liver disease. The five-year cumulative incidence of progression to a decompensated state is approximately 20%, and patients with decompensated cirrhosis have only a 14–35% probability of survival at five years[15].

All CHB patients with impaired liver function are considered for anti-retroviral therapy with the aim of inhibiting HBV replication, facilitating seroconversion and therefore preventing progression to a decompensated state. Antivirals may be used to delay or to prevent the need for transplantation and to reduce the risk of HBV recurrence on the graft[12]. Interferon-alpha is used for treatment of CHB but is contraindicated in decompensated liver disease[15]. Instead, nucleoside/nucleotide analogues, which act by inhibiting the reverse transcriptase responsible for HBV replication, are recommended[15]. Treatment for patients at a decompensated stage has been shown to improve liver function (potentially returning to a compensated state) and decrease mortality[16].

2.2 Comparators

In addition to the therapy under consideration (tenofovir disoproxil fumarate [TDF; a prodrug of tenofovir]), nucleoside/nucleotide analogues currently licensed for use in patients with decompensated liver disease are:

- Entecavir (ETV)[17]
- Adefovir dipivoxil (ADV)[18]
- Lamivudine (in combination with another antiviral drug without cross-resistance to lamivudine)[19]

The Welsh Medicines Partnership (WMP) requested ETV and lamivudine as comparators to TDF (see section 3.2 WMP critique).

2.3 Guidance and related advice

- AWMSG recommended tenofovir (Viread®▼) for use within NHS Wales for the treatment of CHB in adults with compensated liver disease (2008)[20]. This guidance was superseded by NICE in 2009[21]:
- NICE technology appraisal guidance 173: Tenofovir disoproxil for the treatment of chronic hepatitis B. 2009[21].
    - This guidance document recommends TDF as an option for CHB patients with compensated liver disease only[21].
- European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B. 2009[15].
    - These guidelines recommend ETV or TDF as first-line monotherapies for CHB patients. This extends to patients with decompensated liver disease; however EASL note the lack of safety data for these agents in this population[15].
- NICE technology appraisal guidance 96: Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. 2006[14].
    - This guidance document recommends ADV as an option with restrictions for the treatment of CHB (refer to guidance for full details of restrictions)[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence

The company submission included 48-week results from a phase II, double-blind, multicenter, randomised, 168-week study comparing TDF alone, emtricitabine (FTC)/TDF in combination and ETV alone for CHB patients with decompensated liver disease[4,16]. Inclusion criteria were HBV DNA ≥ 10^3 copies/ml, a Child–Turcotte–Pugh (CTP) score of 7–12 (or prior CTP score ≥ 7 and CTP ≤ 12 at screening), ALT < 10 times upper limit of normal and no evidence of hepatocellular carcinoma (see Glossary for further information). Exclusion criteria included positive serologies for human immunodeficiency virus, hepatitis C virus or hepatitis D virus, prior TDF or ETV exposure, and ≥ 24 month ADV exposure. Patients (n = 112, 18 to 69 years) were switched from their current therapy, 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]) and stratified according to CTP score and prior lamivudine exposure. Of 112 patients, 73 (65.2%) were HBeAg-negative at baseline. The groups were balanced in terms of prior lamivudine or ADV exposure: between 36% and 42% of patients had received prior lamivudine therapy and approximately 20% of patients had received prior ADV treatment in each arm. Patients who met certain criteria could, at the investigators discretion, cross-over to open-label FTC/TDF and continue in the study[4,16].

The primary endpoints in this study were related to safety; efficacy parameters were measured only as secondary endpoints, with none of the latter being statistically powered[4,16]. The efficacy parameters measured included HBV DNA and ALT levels, HBeAg/HBsAg loss and seroconversion, and CTP and model for end-stage liver disease (MELD) scores (see Glossary for further information). In addition, resistance surveillance via phenotyping was carried out at baseline and again for viraemic patients at week 48 or earlier. The submission included analysis of all patients who had received at least one dose of study drug. Eighty-eight patients completed 48 weeks of double-blinded treatment, with non-completers regarded as failures. Ten patients switched to open-label FTC/TDF and 14 discontinued study drug. Undetectable HBV DNA levels (< 400 copies/ml) were achieved in 70.5%, 87.8% and 72.7% of patients in the TDF, FTC/TDF and ETV treatment arms, respectively (76.7%, 87.8% and 85.7%, respectively, including patients who crossed-over to open-label). Normalised ALT levels were observed in 46%, 64% and 41% of patients in each of the respective treatment arms. Three patients receiving TDF and four receiving FTC/TDF achieved HBeAg loss and of these seven, five seroconverted. No patients receiving ETV presented HBeAg loss or seroconversion. At week 48, the mean change in CTP score was a decrease of around one for each study group. Median MELD scores were decreased by two for all patients in each of the treatment groups at week 48 compared with baseline. Resistance surveillance of thirteen patients (8 TDF, 2 FTC/TDF, 3 ETV) found no evidence of development of resistance to any study drug[4,16].

The co-primary endpoints of this study were safety-related: tolerability failure (permanent discontinuation due to a treatment-related adverse event [AE]) and confirmed serum creatinine increase ≥ 0.5 mg/dl or confirmed serum phosphorous < 2.0 mg/dl[16]. Tolerability failure occurred in 4 to 10% of patients and was comparable between treatment groups. One patient in the FTC/TDF group discontinued due to a treatment-related grade two allergy. Four TDF patients, three FTC/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[16].

Most AEs occurring in ≥ 5% of patients were comparable across treatment arms and were consistent with decompensated liver disease. A total of 11, 19 and 5 serious AEs (SAEs) occurred in the TDF, FTC/TDF and ETV treatment arms, respectively, with the most common SAEs reported as gastrointestinal disorders, infections and infestations, and hepatobiliary disorders[4,16]. Two SAEs (one case of abdominal pain in the TDF arm and an allergic reaction in the FTC/TDF arm) were considered related to study drug. A total of six deaths were reported in the 48-week follow-up, none were deemed related to study drug; five were due to disease progression and one was due to unrelated septic shock[16].

The SPC for TDF states that renal failure, renal impairment, elevated creatinine, hypophospataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of TDF[1]. As data are limited for CHB patients at high risk of hepatic or renal AEs (which may include those with decompensated liver disease or CTP score > 9), hepatobiliary and renal parameters should be monitored closely in these patients[1].

3.2 WMP critique

- A considerable problem with long-term nucleoside/nucleotide analogue treatment is the emergence of resistance. Resistance to lamivudine has been shown to occur in 70–80% of patients without HBeAg seroconversion after four years' treatment[22]. Therefore, lamivudine is no longer recommended as monotherapy[15]. Add-on therapy with ADV has been used historically, however it also has a low genetic barrier[3] and its use may be limited by nephrotoxicity[12]. ETV has been shown to be superior in efficacy to both lamivudine and ADV, and development of resistance is low; however it is less efficacious in lamivudine-refractory patients and prior use of lamivudine infers an increased risk of resistance to ETV[16,23]. Emerging data has shown that TDF demonstrates potent and superior antiviral efficacy in both treatment-naive and lamivudine-experienced patients with compensated CHB, with no development of resistance through 144 weeks of therapy[23–25]; however, this is not directly related to the indication under submission.
- The comparators included in the company submission were FTC/TDF in combination (off-label) and ETV alone[4]. The current indication of FTC/TDF is confined to the treatment of HIV infection[26]; however, the Committee for Medicinal Products for Human Use (CHMP) considered this treatment arm important to provide data on the use of FTC/TDF in the treatment of HBV infection, considering the wide off-label use (supported by therapeutic guidelines) of FTC/TDF in HIV–HBV co-infected patients[3]. CHMP further noted that a two-arm study (comparing TDF and ETV) would have allowed a larger sample size and a more robust conclusion to be drawn, but that the use of bi-therapy in patients with decompensated CHB is of interest since viral breakthrough and emergence of resistance can be potentially life threatening in this vulnerable population[3].
- The SPC for ETV recommends a 1 mg dose be prescribed for patients with decompensated liver disease[17]. In addition, lamivudine-refractory patients should receive ETV in combination with a second antiviral agent (which does not share cross-resistance with either lamivudine or ETV)[17]. However, of 22 patients in the ETV group, only nine patients (those with ≥ 6 months of lamivudine exposure and/or history of HBV with lamivudine-resistant mutations) received the 1 mg dose and none received ETV in combination, impeding its use as a comparator[16].
- Data presented display efficacy of TDF irrespective of HBeAg status or viral genotype[3,4]. However, results provided are suggestive of superiority of

FTC/TDF over TDF[3]. Further, the response rate for the FTC/TDF arm may have been underestimated due to an imbalance in the proportion of patients with CTP score ≥ 7 at baseline; 71.1% of patients in the FTC/TDF arm, 62.2% of patients in the TDF arm and 54.5% of patients in the ETV arm had CTP > 7[3,16]. It should be noted, however, that the efficacy results provide only a descriptive analysis and are too limited to enable reliable comparison[3].

- Efficacy parameters were measured as secondary endpoints in the trial described with no statistical evaluation; however CHMP deemed this approach reasonable[3]: CHMP stated that due to the potent virologic activity and high genetic barrier of TDF and ETV, they supersede alternative therapeutic options and are already recommended in therapeutic guidelines. Therefore, by using the most potent drugs in this trial, the risk of suboptimal virological efficacy was limited. The study is mainly aimed at responding to the need for safety data as underlined in the therapeutic guidelines for safely using TDF in decompensated patients. The study was regarded as confirmatory for efficacy[3].
- 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[27]; however in this study, forty patients (35.7%) had a CTP score of < 7 at baseline despite > 7 being an inclusion criterion[3]. The mean CTP score at baseline was 7.4[3]. Additionally, patients with very advanced disease (those with CTP score > 12, variceal bleeding, grade 3–4 hepatic encephalopathy, etc.) were excluded from the study. This may contribute to an interpretation of improved prognosis and may also have resulted in a mortality rate that appears lower (4–9% at week 48) than that reported in a previous study[3]. In addition, CHMP raised concerns that the safety results are hampered by low representation of patients with CTP score of > 9[3].
- The measurement of HBV levels may not be a reliable efficacy endpoint as patients with decompensated liver disease tend to have low or undetectable HBV replication[28].
- Over the 48 weeks, a lower number of patients in the FTC/TDF treatment arm withdrew from the study compared to the TDF and ETV treatment arms (3 [7%], 8 [18%], and 3 [14%], respectively). Five (11%) patients from the TDF arm crossed-over to open-label FTC/TDF, compared with two (4%) from the FTC/TDF arm and three (13%) from the ETV arm.[16].
- A relatively high rate of screening failure was reported in this study; 27 to 29% for the TDF and ETV arms, compared with 11% in the FTC/TDF arm[3].
- Of 112 patients included in the study, 60 (53.6%) were Asian and 47 (42.0%) were white, which would not appear to be representative of the population of Wales[16].

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost–utility analysis (CUA) of first-line TDF compared to first-line ETV, lamivudine, ADV, ADV/lamivudine and best supportive care (BSC) for the treatment of CHB in adults with decompensated liver disease[4]. In these scenarios, if resistance develops to first-line treatment, patients are assumed to switch to BSC. Alternative strategies of the use of TDF as a rescue therapy following development of resistance with the above first-line regimens are also presented.

The company has noted that BSC is not an appropriate first-line treatment strategy and that lamivudine monotherapy is not licensed in the UK for treatment of decompensated disease[4].

The analysis is based on a complex Markov state-transition model, designed for a previous submission for the use of TDF in treatment-naive patients with compensated disease[20]. In the current model, patients enter in a decompensated liver disease state, from which they can proceed to more severe states and death, receive a liver transplant or, during the first year only, can regress to compensated health states. It is assumed there are no differential effects between treatment strategies in the initial decompensated disease state; differential effects are assumed only in subsequent health states in those patients who regress to a compensated disease state. The probabilities of transitions among different health states were derived from published studies in treatment-naive patients with compensated disease, using indirect and mixed treatment comparisons[23]. The model assumes patients are split equally between those with HBeAg-positive and HBeAg-negative disease, and have a mean starting age of 52 years. Lamivudine resistance is assumed to be possible from the start of the model. A one-year cycle length and a lifetime analytic horizon have been adopted (see Appendix 1 for further details).

4.1.2. Results

Results of the CUA of first-line TDF compared to first-line ETV, ADV and ADV/lamivudine, all followed by BSC, and probabilistic analysis using 6,000 model simulations are presented in Table 1.

Table 1. Company-reported results of CUA of TDF versus ETV, ADV and ADV/lamivudine followed by BSC for first-line treatment of CHB in patients with decompensated liver disease.

Base case	TDF	ETV	Difference (TDF vs ETV)	ADV	Difference (TDF vs ADV)	ADV/ lamivudine	Difference (TDF vs ADV/ lamivudine)
Annual drug costs	£2,924	£4,420	-£1,496	£3,683	-£759	£4,701	-£1,777
Total cost	£94,526	£80,091	£14,435	£91,860	£2,666	£117,293	-£22,767
Life years gained	9.5	7.9	1.6	8.9	0.6	9.7	-0.2
Total QALYs	5.50	4.58	0.92	5.13	0.37	5.50	0.00
ICER for TDF versus comparator		£15,747		£7,247		Dominant*	
Probability cost effective at £20,000/QALY gained		67%		79.7%		99%	
Probability cost effective at £30,000/QALY gained		89%		85%		98%	

ADV = adefovir dipivoxil; ETV = entecavir; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TDF = tenofovir disoproxil fumarate
* TDF is less expensive and marginally more effective than ADV/lamivudine
NB: These results relate to the assumption that resistance to lamivudine is possible from the start

One-way sensitivity analyses indicate that the model was most sensitive to discount rates for both costs and outcomes, and the cost of drugs. The company states that this suggests that if the cost of TDF can be reduced this will lead to more favourable cost effectiveness results. The probability of e-seroconversion in lamivudine-resistant patients and the probabilities of regression to compensated disease and progression to more severe states were also influential, as would be expected.

A wide range of scenario analyses were conducted around the analyses of first-line TDF use, which demonstrate the model's sensitivity to several assumptions. The incremental cost effectiveness ratio (ICER) decreases as the probability of regression to compensated disease increases, which is an important finding as the probability assumed in this model has been increased from 13.57% in the original compensated disease model to 36.65% in the current model. At the original probability, the ICERs for TDF versus ADV and ETV increase to £14,500 and £22,800, respectively. Treatment with TDF is cost saving compared to ETV and ADV when TDF resistance rates are assumed to be the same as those for ETV and ADV, respectively. The assumption of an equal split between HBeAg-positive and HBeAg-negative patients has little impact on the model outputs, although this could be due to the limitations of data available for modelling.

Relaxing the assumption of lamivudine resistance being possible from the start of the model (which the company considers is less representative of current clinical experience due to most patients having received prior lamivudine therapy), results in a doubling of the ICER for first-line TDF versus ADV, but TDF is reported to be both less costly and more effective than ETV and ADV plus lamivudine first-line treatment strategies.

Analyses of alternative scenarios, including the use of TDF as second-line treatment, are provided in Table 2, Appendix 1. Based on the current model, the use of TDF as rescue therapy rather than BSC following failure of first-line treatment with lamivudine, ADV or ETV monotherapy generated an ICER below £30,000. First-line use of TDF followed by BSC was both less effective and less costly than its use as rescue therapy following failure of first-line ADV or ETV monotherapy, or ADV/lamivudine combination therapy (see Table 2, Appendix 1).

4.1.3 WMP critique

Strengths of the economic evidence include:

- A number of treatment strategies were considered for the treatment of CHB in adults with decompensated liver disease.
- The company has conducted literature reviews to update their original model with relevant data specific to decompensated disease states.
- A wide range of sensitivity and scenario analyses have been presented.

Limitations of the economic evidence include:

- The data available to model decompensated disease and relative efficacy estimates for different treatment strategies remain limited. Rates of progression of patients from decompensated disease to more severe states, and rates of regression to compensated disease are assumed equal, irrespective of treatment received, and the data used to inform these rates are derived from small, dissimilar patient groups. Sensitivity analyses indicate the model is sensitive to the assumed rates.
- Modelled differential effects of treatment appear to be driven by compensated disease state data, derived from indirect and mixed treatment comparisons of trials conducted in treatment-naive patients with compensated disease. Indirect data comparisons have a number of inherent limitations, and the extent to which these data would reflect clinical experience of the modelled patient population is unclear. The model is sensitive to assumed resistance profiles, which are derived using a range of assumptions. Collectively, there appears to be significant uncertainty associated with the estimated efficacy of the comparator treatments in patients with decompensated liver disease, and the probability of transition among the different modelled health states.
- Although a wide range of sensitivity analyses have been conducted, these are limited to comparisons of first-line TDF against other first-line strategies. The company has provided analyses to compare the use of TDF as rescue therapy against first-line therapy, but no sensitivity analyses for this strategy have been provided.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of TDF compared to ETV, ADV, ADV/lamivudine or BSC for the treatment of CHB in adults with decompensated liver disease.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT
NOT FOR NMG TO CONSIDER

5.1 Budget impact evidence
5.1.1 Context and methods
According to the company submission, there are no official figures for the number of decompensated liver failure patients in Wales[4]. Based on expert opinion, the company estimates there are fewer than ten patients with decompensated CHB liver disease in Wales. The company assumes that the incidence of CHB in adults with decompensated liver disease in Wales is 0 to 4 patients per year. The number of patients prescribed TDF is expected to be 4 to 8 people a year, with the remainder assumed to be treated with ETV. The estimated numbers of patients treated with TDF and the associated costs over the five-year period are shown in Table 2. The company assumes costs will largely be unchanged, as most decompensated patients will already be receiving treatment. The budget impact analysis presents net cost savings associated with the use of TDF in place of ETV.

Table 2. Company-reported costs associated with TDF treatment.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	10	12	14	16	18
Number of patients anticipated to be treated with TDF	8	10	12	14	16
TDF costs	£23,392	£29,240	£35,088	£40,936	£46,780
Net annual cost saving from use of TDF instead of ETV	**£11,968**	**£14,960**	**£17,952**	**£20,944**	**£23,936**
ETV = entecavir; TDF = tenofovir disoproxil fumarate					

5.1.2 WMP critique of the company's budget impact estimates
There is a lack of reliable data with which to estimate eligible patient numbers, and hence budget impact estimates. Estimation of the number of eligible patients is based on expert opinion; however, few details are provided. ADV alone or in combination with lamivudine are not considered as potential comparators. The budget impact estimates would therefore seem subject to uncertainty, but the company notes that the cost impact is likely to be marginal.

5.2 Comparative unit costs

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

Regimen	Example of daily doses	Cost per patient per year
Viread®▼ (TDF) 245 mg tablets	245 mg once daily	£2,926
Hepsera® (ADV) 10 mg tablets	10 mg once daily	£3,610
Baraclude® ▼ (ETV) 0.5 and 1 mg tablets	1 mg once daily	£4,420
Zeffix® (lamivudine) 100 mg tablets	100 mg daily in combination with another antiviral drug without cross-resistance to lamivudine.	£1,018
ADV = adefovir dipivoxil; ETV = entecavir; TDF = tenofovir disoproxil fumarate *Costs are based on BNF[29] and/or MIMS[30] list prices NB: This table does not imply therapeutic equivalence of drugs or the stated doses. Combination therapy may be required in some patients depending on treatment experience and resistance. See individual SPCs for full prescribing details[1,17–19].		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

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

6.2 Ongoing studies

The company submission states that the trial described is ongoing and that final results will be reported on conclusion of the study, at 168 weeks[4].

GLOSSARY

Alanine aminotransferase (ALT): ALT is found predominantly in hepatocytes where it participates in the alanine cycle by catalysing the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate[31,32]. Where hepatocellular damage has occurred, ALT levels in the blood become elevated; hence, blood ALT is used as a marker for hepatocellular injury. Active CHB is associated with either persistent elevation of ALT or an erratic pattern of ALT changes, with flare-ups resembling acute hepatitis B that can be severe or even fatal.

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[33,34]. 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)[35,36].

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[37]. The presence of HBeAg in a host's serum is typically associated with very high rates of viral replication and enhanced infectivity[15]. During the natural 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[15].

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. The variables considered are:

- Serum bilirubin
- Serum creatinine
- INR for prothrombin time

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

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

The result is interpreted as in Table 2[38].

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[4].

	Base case model	Appropriate?
Comparator(s)	TDF monotherapy is compared against ADV, ETV, lamivudine, ADV/lamivudine or BSC as first-line treatment of decompensated liver failure. If resistance develops to first-line treatment, patients are assumed to switch to BSC. Alternative strategies of the use of TDF as a rescue therapy following development of resistance with the above first-line regimens are also presented.	WMP requested comparison against ETV and lamivudine. Lamivudine monotherapy is not indicated for patients with decompensated liver failure in the UK due to the potential for development of resistance; lamivudine is licensed only for use in decompensated liver disease in combination with a second agent without cross-resistance to lamivudine[1]. The company notes that lamivudine monotherapy and BSC are not recommended as first-line treatment approaches for decompensated liver disease. The company has indicated that the target population is patients using TDF as a first-line treatment.
Population	Adult patients with CHB and decompensated liver disease (assumed to be split equally between those with HBeAg-positive and HBeAg-negative disease).	Yes, in line with the licensed indication[1]. The model assumes the average age of a patient with decompensated liver disease to be 52 years, based on the median age of patients randomised to TDF in the key phase II trial in patients with decompensated liver disease[16].
Analysis type	CUA of TDF 240 mg followed by BSC (if resistance develops) versus the comparators above. The analysis is undertaken using a complex Markov model developed originally for the use of TDF in patients with compensated liver disease[20]. For the current submission, patients enter the model with decompensated disease from where they may progress to liver transplant, HCC or death, or during the first year only they may regress to compensated disease.	CUA is the preferred type of analysis.
Perspective	Considers direct medical costs only, from the perspective of NHS Wales.	Yes.
Time Horizon	The base case analysis assumes a lifetime horizon (42 years). Sensitivity analyses considered alternative time horizons of 5, 10, 20 and 30 years.	A lifetime time horizon would be appropriate. The base case model is reported to assume a 42-year lifetime horizon as this was the time horizon adopted in the original model for compensated disease (which was based on life expectancy for patients of mean age 38 years)[20]. One-way sensitivity analyses demonstrated that ICERs are relatively insensitive to a reduction in time horizon to 30 years, and for shorter time horizons the ICER decreases for the comparison of TDF then BSC versus ADV then BSC, and versus ETV then BSC.

Table 1. Continued

	Base case model	Appropriate?
Discount rate	For base case analysis a 3.5% p.a. discount rate is applied to both costs and outcomes. Sensitivity analysis considers discount rates of 0% for costs and benefits, and also costs discounted at 6% and benefits at 1.5%.	Yes. Both costs and outcomes were very sensitive to discount rates.
Efficacy	Efficacy parameters include HBV DNA suppression, HBeAg/HBsAg loss and seroconversion, and those assumed in the previous submission for compensated liver failure patients[20] have been updated with data from a literature review. The model assumes patients may regress from decompensated to compensated disease during the first year. The probability of regression from decompensated disease to compensated disease is based on a simple weighted average of point estimates derived from studies of TDF, ETV and lamivudine in patients with decompensated disease. These transition probabilities are applied equally to all treatment regimens (i.e. there are no differential effects of treatment modelled). Once in a compensated disease state, transitions among subsequent health states are largely unchanged from the original submission. Efficacy data for the original model were derived from Bayesian mixed treatment comparisons[20,23,39], which included direct comparative data, where available, along with indirect comparisons. Progression from decompensated disease to death or HCC are also based on weighted average of several trials conducted in patients with decompensated disease. Resistance rates, which determine switching of treatment, are based on rates assumed in the original model for compensated disease. As no resistance to TDF was reported after four years of surveillance, the resistance rates were assumed to be <0.23%.	No differential effects of treatment appear to be modelled at the start of the model for patients with decompensated disease. Differential effects of treatment therefore appear to be driven mainly by the relative efficacy of treatments in the compensated disease states and the health states that follow this. For the compensated disease states and subsequent states, efficacy parameters were derived from studies involving treatment-naive patients with HBeAg-positive CHB and compensated liver disease[23]. However, the model presented in the current submission includes both HBeAg-positive and HBeAg-negative patients who have/have had decompensated liver disease that may have already developed drug resistance. The relative efficacy data for the comparators are derived from mixed treatment comparisons, which include direct and indirect comparative trial data. Results of indirect comparisons have inherent limitations, and several assumptions were made in the absence of complete data for the network of evidence for all comparators. The probabilities of regression from decompensated to compensated disease and the probability of progression to death, are derived as a weighted average of phase II trial data for TDF in decompensated disease[16] and other trial data relating to ETV and lamivudine. TDF was licensed for use in decompensated disease on the basis of the phase II trial data[16], although efficacy was a secondary endpoint in that trial. The company submission notes that the number of patients informing these weighted average estimates from was small, and patient populations were dissimilar. The assumption of no differential effects of treatment upon the probability of regression to compensated disease would therefore seem uncertain. A range of assumptions were used in the original submission to model resistance, which also apply to the current analysis. Collectively, there appears to be significant uncertainty associated with the estimated efficacy of these comparator treatments in patients with decompensated liver disease, and the probability of transition between the different modelled health states.

Table 1. Continued

	Base case model	Appropriate?
Adverse effects	No adverse events have been modelled.	It is implicitly assumed that there are no differential adverse effects between any treatments, including between antiviral treatment and BSC.
Utility values	No HR-QoL data were collected during TDF/ADV/ETV/lamivudine trials involving patients with chronic hepatitis B. Utility values for patients with CHB were taken from a published study[40].	Seems appropriate. A range of assumptions about utility weights for different health states (in particular for HBeAg-negative patients) have been made due to lack of data, but one-way sensitivity analyses suggest the model outputs are relatively insensitive to the utility values in the range explored.
Resource use and costs	The treatment costs included costs of drugs, tests and outpatient visits. The costs of treatment for the different health states, including compensated cirrhosis, decompensated liver failure, HCC, liver transplant and post-transplant follow-up were taken from the previous submission in compensated liver failure patients[20], and have been inflated to 2010 costs.	The costs of treating different health states used in the model were for 2006–2007, many of which related to the management of hepatitis C. The company considers that the costs health states would be comparable, and these costs have been inflated to 2010; however, more recent unit cost data are available. Antiviral drug costs are based on current MIMS and/or BNF price lists.
Uncertainty and scenario analyses	Uncertainty of the model estimates was addressed using a number of sensitivity and scenario analyses. One-way deterministic analyses were conducted to assess the uncertainty associated with input parameters, including cost of drugs, discount rates, transition probabilities between different health states, costs and utilities associated with different health states, and rates of developing drug resistance. Scenario analyses for different treatment strategies included variation in the number of HBeAg-positive and HBeAg-negative patients, disease management costs, time horizon, mortality rates, drug resistance rates, and the time of resistance onset. Probabilistic sensitivity analysis was conducted for the base case scenarios to demonstrate the probabilities of TDF being cost-effective at thresholds of £20,000 and £30,000 per QALY gained.	An appropriately wide range of sensitivity and subgroup analyses have been performed. However one-way sensitivity analyses are limited to the comparisons of first-line TDF then BSC against first-line ADV, ETV and lamivudine monotherapy, and no sensitivity analyses are provided for the use of TDF as rescue therapy.
Model Provided?	Yes	Yes

ADV = adefovir dipivoxil; BSC = best supportive care; CHB = chronic hepatitis B; CUA = cost–utility analysis; ETV = entecavir; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B s antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HR-QoL = health-related quality of life; ICER = incremental cost effectiveness ratio; TDF = tenofovir

Table 2. Summary results of all base case cost utility analyses (assuming lamivudine resistance is possible from the start).

				First-line TDF	TDF as rescue therapy following resistance to first-line treatment			
	Treatment strategy	Total costs per patient	Total QALYs per patient	ICER for TDF then BSC versus comparator	ICER for ADV then TDF versus comparator	ICER for ETV then TDF versus comparator	ICER for lamivudine then TDF versus comparator	ICER for ADV/lamivudine then TDF versus comparator
	Lamivudine then BSC	£55,109	3.99	£26,055	£26,809	£24,318	£15,493	£40,695
	ETV then BSC	£80,091	4.58	£15,747	£18,892	£15,622	£1,884	£39,931
	ADV then BSC	£91,860	5.13	£7,247	£16,511	£10,758	DOMINANT†	£65,500
First-line TDF	TDF then BSC	£94,526	5.50	-	£31,985	£15,227	DOMINANT†	£807,670
	ADV/lamivudine then BSC	£117,293	5.50	DOMINANT‡	DOMINANT†	DOMINANT†	DOMINANT†	£16,798
TDF as rescue therapy following resistance to first-line treatment	Lamivudine then TDF	£82,271	5.74	DOMINATED*	DOMINATED¶	£342,140	-	DOMINATED¶
	ETV then TDF	£98,928	5.79	£15,227**	DOMINATED¶	-	£342,140††	DOMINATED¶
	ADV then TDF	£101,570	5.72	£31,985**	-	DOMINANT†	DOMINANT†	DOMINATED¶
	ADV/lamivudine then TDF	£117,848	5.53	£807,670**	DOMINANT†	DOMINANT†	DOMINANT†	-

ADV = adefovir dipivoxil; BSC = best supportive care; ETV= entecavir; ICER= incremental cost effectiveness ratio; TDF=tenofovir
‡ TDF then BSC as first-line therapy is both less costly and marginally more effective versus the comparator
*TDF then BSC as first-line therapy is both more costly and less effective versus the comparator
**TDF then BSC as first-line therapy is both less effective and less costly than the comparator – ICER represents cost saved per QALY foregone
†TDF as rescue therapy is both less costly and more effective than the comparator
††TDF as rescue therapy is both less effective and less costly than the comparator – ICER represents cost saved per QALY foregone
¶TDF as rescue therapy is both more costly and less effective than the comparator
NOTE: Lamivudine monotherapy regimens are not recommended as treatment strategies in decompensated liver disease