All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

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NICE GUIDANCE ISSUED JULY 2009

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Final Appraisal Report

Tenofovir disoproxil fumarate (Viread®) for the treatment of hepatitis B

Gilead Sciences

Advice No: 1208 – August 2008

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Recommendation of AWMSG

Tenofovir (Viread®) is recommended for use within NHS Wales for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

AWMSG is of the opinion that tenofovir (Viread®) should be initiated only by healthcare professionals experienced in the management of viral hepatitis; however continued care may be suitable for provision under shared care arrangements.

Note (posted 8/12/08):
The conclusion reached by the Interface Pharmacist Group and endorsed by AWMSG was that tenofovir (Viread®) is not suitable for shared care within NHS Wales

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 13th August 2008

The recommendation of AWMSG is:

Tenofovir (Viread®) is recommended for use within NHS Wales for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

AWMSG is of the opinion that tenofovir (Viread®) should be initiated only by healthcare professionals experienced in the management of viral hepatitis; however continued care may be suitable for provision under shared care arrangements.

Additional information:

- There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus
- Due to the risk of development of HIV resistance, tenofovir should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Tenofovir (Viread®) is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis[1].

2.2 Dosing:
The recommended dose for the treatment of chronic hepatitis B is 245 mg (one tablet) once daily taken orally with food.

Each tablet of 245mg of tenofovir disoproxil (as fumarate) is equivalent to 300mg of tenofovir disoproxil fumarate.

Treatment with tenofovir disoproxil fumarate may be discontinued if there is hepatitis B surface antigen (HBsAg) loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown[1].

Therapy should be initiated by a physician experienced in the management and/or treatment of chronic hepatitis B.

2.3 Market authorisation date: 24th April 2008[2]

2.4 UK Launch date: 2 May 2008[2,3]

3.0 DECISION CONTEXT

Chronic hepatitis B is defined as viraemia and hepatic inflammation that persists for more than six months after acute infection with hepatitis B. The risk of chronic infection depends on the nature of the immune response to the initial infection. About two to ten percent of people who are infected as adults go on to develop chronic hepatitis B[4].

The prevalence of chronic hepatitis B is estimated to be between 0.2 and 0.3% of the UK population. There are around 7,000 to 7,700 new cases of chronic hepatitis B in England and Wales each year, mainly due to immigration[5]. The company estimates that 3,873 patients may be eligible for treatment in Wales and that 15 are likely to receive treatment with tenofovir[3].

Diagnosis is based on the presence of serological markers in the blood; hepatitis B viral (HBV) DNA is present in both acute and chronic hepatitis B. HBsAg is a viral protein detectable in the blood in both acute and chronic infection. Hepatitis B early antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg. Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted. People with active chronic hepatitis B are at increased risk of liver cirrhosis and hepatocellular carcinoma (HCC)[4].

Active disease is characterised by elevated HBV DNA concentrations, raised ALT and aspartate transferase (AST), hepatic necrosis and inflammation on biopsy. Liver damage due to infection and inflammation may lead to cirrhosis. Progression to cirrhosis occurs at an annual rate of 2 to 5.5% with a cumulative five year rate of progression of 8 to 20%. For those with the HBeAg-positive form of the disease a further flare up of the disease leads to the development of antibodies against the early antigen, referred to as HBeAg seroconversion. Most people then remain in an inactive

HBsAg carrier state. Seroconversion is associated with good quality of life and a relatively low risk of disease progression. People can be infected with the HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form. Infection with HBeAg-negative chronic hepatitis B is associated with a fluctuating course and a poor prognosis. Active disease 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. Few patients with HBeAg-negative chronic hepatitis B achieve a lasting remission. Progression to cirrhosis of the liver has been estimated to occur in eight to ten percent of people with HBeAg-negative chronic hepatitis B each year[4].

Chronic carriers of the hepatitis B virus with abnormal liver function tests should be considered for antiviral therapy[5]. The aim of treatment is to prevent progression to cirrhosis or HCC by suppressing HBV DNA levels[6] and facilitating seroconversion[5].

Current treatment options are only effective in around 40% of patients, and they are often associated with limited efficacy, poor tolerability or resistance problems[5]. Anti-viral resistance may develop after prolonged monotherapy and rebound hepatitis can occur if the agent is stopped or if resistance ensues[7]. It is estimated that resistance to lamivudine is >60% after three to four years of treatment[4,5]. Interferon alfa and peginterferon alfa-2a may be used first-line depending upon the patient and type of hepatitis B. Both have a predefined treatment course but can be poorly tolerated. Adefovir (alone or in combination with lamivudine) is effective in lamivudine-resistant and interferon-resistant disease and is recommended by the National Institute for health and Clinical Excellence (NICE) as a suitable option where lamivudine and interferon have failed or are unsuitable[4]. Final appraisal determination from NICE recommends entecavir but not telbivudine in the treatment of chronic hepatitis B mono-infection[8,9].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Based on two randomised controlled trials (RCTs), tenofovir monotherapy demonstrated greater efficacy than adefovir monotherapy in terms of a primary composite endpoint of viral DNA suppression below 400 copies/ml and histologic improvement for patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. This was mainly due to its efficacy on viral suppression; both drugs produced similar results with regard to histologic improvement and normalisation of ALT at week 48. HBeAg loss and seroconversion were comparable between drug treatments in HBeAg positive patients. Adverse events were comparable for both drugs. The majority of patients were treatment-naïve and patients were excluded if they had co-infection with hepatitis C, hepatitis D or human immunodeficiency virus (HIV). Though no cases of drug resistance were reported in the tenofovir arms further long-term data are required to support these findings.

4.2 Review of the evidence on cost-effectiveness

A complex Markov model has been developed to compare tenofovir, adefovir, entecavir, lamivudine and the most commonly used combinations of these in a simulated cohort meeting the tenofovir licensed indication. Direct comparative data for tenofovir exists only in first-line use as monotherapy against adefovir; therefore, data from several sources have been derived and combined using a range of methods in order to model comparative efficacy and development of resistance for the many different possible treatment strategies. This has required a wide range of assumptions

to be made. Lamivudine followed by no treatment has been used as the relevant comparator for tenofovir treatment strategies, as other potential comparators were technically dominated (i.e. most other strategies were more expensive and/or less effective and would not be considered cost effective compared with these strategies). However, in practice lamivudine followed by no treatment is unlikely to be an appropriate treatment strategy in the patient population being considered.

In the overall patient population that is modelled, base case results indicate that tenofovir monotherapy as the first-line treatment is associated with the lowest incremental costs per Quality Adjusted Life Year (QALY) versus lamivudine followed by no treatment (range £9,096 to £9,490) out of all the first-line strategies considered. Furthermore, all strategies involving tenofovir monotherapy as the first-line treatment have lower incremental costs per QALY than all strategies involving tenofovir as a second-line treatment. The total discounted costs and QALYs for first-line tenofovir treatment are both higher than for second-line tenofovir treatment in all sub-groups considered. The incremental costs per QALY for first-line tenofovir use compared directly against second-line tenofovir use ranged from £4,629 to £10,773.

5.0 LIMITATIONS OF DECISION CONTEXT

- The company acknowledge that there is a lack of long-term efficacy and safety data in treatment naive individuals with chronic hepatitis B. However, the two main RCTs are to be followed up over eight years.
- There is a lack of randomised controlled data in lamivudine-resistant patients with hepatitis B mono-infection or in patients with decompensated liver disease.
- Tenofovir (monotherapy) has only been compared to adefovir (monotherapy) in RCTs, RCT data for other comparators (as monotherapies) are currently unavailable. Trials are in progress for tenofovir combination therapy.

6.0 CLINICAL EVIDENCE

The company submission is primarily based on two RCTs, both in patients with chronic hepatitis B mono-infection. Patients were ineligible for trial entry if they were co-infected with hepatitis C, hepatitis D or human immunodeficiency virus (HIV). Studies 0102 and 0103 were carried out in patients with HBeAg-negative and HBeAg-positive disease, respectively[10,11]. The majority of patients were from Europe (study 0102: 62%, study 0103: 55%)[3]. See Appendix 1 tables 1 and 2 for further details of the trials. A further study (0106) is included comparing tenofovir monotherapy with combination tenofovir and emtricitabine therapy, interim data are provided in the submission as a clinical report for those patients who have received at least 24 weeks of treatment[12].

6.1 Clinical efficacy:

6.1.1 Tenofovir as monotherapy for the treatment of chronic hepatitis B

The primary efficacy parameter (for studies 0102 and 0103) was the proportion of subjects who achieved a composite virological and histologic response at week 48. Complete response was defined as suppression of HBV DNA below 400 copies/ml and at least a two-point reduction in the Knodell necroinflammatory score without worsening in the Knodell fibrosis score (from week 44-48 liver biopsy)[3,10,11]. The primary analysis included those who received at least one dose of study medication (randomised and treated [RAT] analysis set). Results at week 48 are presented tables 1 and 2 and in Appendix 1, tables 1 and 2

After week 48 patients could go on to receive open label tenofovir 300mg daily and after week 72 additional emtricitabine (200mg daily) was permitted if HBV DNA was greater than or equal to 400 copies/ml. Treatment follow up is for eight years.

Results:

Table 1. Primary efficacy response outcomes and components at Week 48 for Study 0102 (RAT analysis set) [3]

Response category	Tenofovir (n=250) (n %)	Adefovir (n=125) (n %)	Difference estimate (95% CI)*	P-value
Complete response				
Yes	177 (70.8)	61 (48.8)	23.5% (13.2 to 33.8)	<0.001
No	73 (29.2)	64 (51.2)		
Histologic response				
Yes	181 (72.4)	86 (68.8)	5.2% (-4.5 to 14.9)	0.293
No	69 (27.6)	39 (31.2)		
HBV DNA <400 copies/ml				
Yes	236 (94.4)	80 (64.0)	30.3% (21.6 to 39.1)	<0.001
No	8 (3.2)	41 (32.8)		
Missing	6 (2.4)	4 (3.2)		

*adjusted for baseline ALT stratum

Week 72 data (HBeAg-negative chronic hepatitis B)
After 24 weeks of tenofovir, 96% (108/112) of patients initially randomised to adefovir had HBV DNA <400 copies/ml. Of those randomised to tenofovir, HBV DNA remained at <400 copies/ml in 222 of the 235 continuing therapy; data were missing for nine subjects.

Table 2. Primary efficacy response outcomes and components at Week 48 of Study 0103 (RAT analysis set) [3]

Response category	Tenofovir (n=176) (n %)	Adefovir (n=90) (n %)	Difference estimate (95% CI)*	P-value
Complete response				
Yes	177 (66.5)	11 (12.2)	54.1% (44.6 to 63.6)	<0.001
No	59 (33.5)	79 (87.8)		
Histologic response				
Yes	131 (74.4)	61 (67.8)	5.8% (-5.6 to 17.2)	0.320
No	45 (25.6)	29 (32.2)		
HBV DNA <400 copies/ml				
Yes	140 (79.5)	12 (13.3)	65.9% (56.8 to 75.0)	<0.001
No	29 (16.5)	74 (82.2)		
Missing	7 (4.0)	4 (4.4)		

*adjusted for baseline ALT stratum

Further results are provided in Appendix 1.

Points to note:

- Study 0103 excluded patients who had ALT levels between one and two times the ULN, though these patients may be considered eligible for treatment.

6.1.2 Tenofovir as combination therapy for the treatment of chronic hepatitis B

A 96 week study is currently ongoing in which tenofovir 300mg daily and emtricitabine / tenofovir placebo is being compared with tenofovir 300mg / emtricitabine 200mg daily and tenofovir placebo. Patients have been switched from prior therapy with adefovir which they had received for at least 24 weeks but no more than 96 weeks. Safety data are available up to week 24 for all randomised and treated patients (n=105) and efficacy data is said to be provided for a subset of patients (n=64). Patients are HBeAg-negative (less than 30% of group) or HBeAg-positive (over 70% of group) or for at least six months have been HBsAg-positive (not stated). Over half of patients had previously received lamivudine and 17.7% of those showed lamivudine-resistant mutations. The primary efficacy endpoint is suppression of HBV DNA levels below 169 copies/ml at week 48, though the interim results presented are to week 24. At week 24 data are only supplied for 60 patients; of these patients 37 (61.7%) attained HBV DNA levels below 169 copies/ml, though the data provided does not appear to break this down by treatment group[12].

Points to note:

- No patients from the UK have been enrolled in study 0106

6.2 Safety:

As tenofovir is excreted renally, plasma concentrations of tenofovir will increase for those individuals who have impaired renal function. Dose adjustment is therefore required in those with moderate to severe renal impairment. The company recommends that creatinine clearance should be calculated in all patients prior to starting therapy with tenofovir and renal function should be monitored every four weeks during the first year, and then every three months. This requires four additional blood tests in the first year (depending on local clinical practice). Patients with renal impairment may require closer monitoring[3].

Study 0102: Safety analysis included all patients who have received at least one dose of study medication. Arthralgia occurred more frequently with tenofovir (6%) versus adefovir (0%), p=0.003, though this was generally mild to moderate in severity and in the majority of cases was considered by the investigators to be unrelated to tenofovir therapy (ref 0102)[3,10]. The frequency of drug-related adverse events and serious adverse events were comparable between groups.

Study 0103: Safety analysis included all patients who have received at least one dose of study medication. The incidence of drug-related adverse events was higher with tenofovir (30.7%) compared with adefovir (16.7%), p=0.018. Gastrointestinal disorders were more frequently reported in the tenofovir group (13.6% versus 1.1%; p<0.01) and were mainly due to reports of mild nausea[3,11].

The safety analyses suggest that there are no additional safety concerns identified with the use of tenofovir in patients treated for hepatitis B when compared to data from HIV-infected patients who received tenofovir.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications:

- Lamivudine
- Adefovir
- Entecavir
- Combinations of the above agents

Interferon and peginterferon were not considered in any indirect comparisons within the company submission as these are generally given earlier in the treatment pathway to a different subgroup of patients[3]. At this stage it is unlikely that the use of tenofovir would replace interferon and peginterferon in Welsh clinical practice[3].

There are no head to head RCTs of tenofovir versus lamivudine, entecavir or telbivudine in patients with hepatitis B mono-infection.

Expert interviews conducted by the company suggest that telbivudine is occasionally used at some centres, but is substantially less widely used than lamivudine, entecavir or adefovir.

At the time of preparation of this report the final appraisal determination recommendations from NICE are that telbivudine is not recommended for the treatment of chronic hepatitis B[8]. NICE recommendations for entecavir are as a treatment option for HBe-Ag-positive or negative chronic hepatitis B[9].

7.2 Comparative effectiveness:

- Adefovir would appear to be an appropriate comparator given that it is structurally similar to tenofovir and is likely to be considered for similar patient groups.
- The company acknowledge that the majority of the safety and efficacy data for tenofovir in hepatitis B has been undertaken in treatment-naive patients[3].
- Pooled analysis of the results of studies 0102 and 0103 suggest that virologic response to tenofovir was comparable between those patients who had previously received lamivudine and those were treatment naive.
- Data from non-randomised studies in lamivudine-resistant patients indicate that after a year of therapy with tenofovir, over 40% of patients had undetectable HBV DNA levels.
- The company submitted a pooled analysis of resistance data for lamivudine, entecavir, adefovir and tenofovir (see Section 8.3.5.1 for further details). Results were separated according to those who were treatment-naive, those who were lamivudine-resistant and those who received combination therapy. Pooled annual risk of resistance was calculated from the total number of patients with reported resistance for that year divided by the total number of patients monitored in that year. For tenofovir and combination therapy there were relatively few long-term studies that included more than 100 patients. For treatment-naive patients, the tenofovir rates were extrapolated from year one data; since no cases of virologic resistance have yet been identified, the risk of developing tenofovir resistance was based on the assumption that one hypothetical patient would develop virologic resistance to tenofovir each year. The lamivudine-resistant data were provided from a small retrospective study. For the other therapies included (lamivudine, adefovir and entecavir), follow up data were available for between three and five years. Overall tenofovir was associated with the lowest cumulative resistance for both treatment-naive and lamivudine-resistant groups. Given the limitations of the follow up data and that the methods used to measure resistance varied between studies, the results should be viewed with caution.
- The company state that tenofovir has no cross-resistance with lamivudine, entecavir, emtricitabine or telbivudine and therefore may be effective in patients who have shown resistance to these medications and/or may be given in combination to reduce the risk of resistance further. Study 0106 compares tenofovir alone and in combination with emtricitabine in adefovir-experienced

patients. Early results are encouraging, though too limited to draw firm conclusions.

- Viral resistance testing may be used to facilitate the choice between tenofovir and another treatment, although the extent to which resistance testing would be used in clinical practice is uncertain.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

Additional commercial in confidence data was provided to AWMSG members.

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by the use of tenofovir justify any associated increase in costs over the relevant comparators and, if so, whether the total budgetary impact of supporting the use of tenofovir is acceptable.

8.2 Review of published evidence on cost-effectiveness

There are several published studies of the cost-effectiveness of other antiviral agents[3], but standard searches conducted by WMP have not identified any published evidence on the cost effectiveness of tenofovir in the treatment of non-HIV-infected patients with chronic hepatitis B.

The company submission briefly contrasts the current model outputs for strategies of lamivudine versus best supportive care (BSC) and first-line use of adefovir versus second-line use with those of other models submitted to NICE[4] and Scottish Medicines Consortium[13] in support of adefovir. The current model estimates lamivudine to be less cost effective versus BSC, and first-line adefovir to be substantially more cost effective versus second-line use than the previous models have. The company submission states that this is likely to be because of more accurate modelling of resistance in the current model, in addition to the differences in the data inputs used[3]. However, the current model and analyses rely on a range of assumptions and extrapolations, particularly around resistance rates, as discussed in Section 8.3.5.1.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission[3] describes a cost utility analysis of tenofovir in adults with HBeAg-positive or HBeAg-negative chronic hepatitis B who have compensated liver function, evidence of active viral replication, persistently elevated serum ALT or histologically active disease (patients meeting the licensed indication)[1]. A Markov model has been developed and run using cohort simulation to compare tenofovir, adefovir, entecavir, lamivudine and the most commonly used combinations of these (adefovir plus lamivudine, entecavir plus adefovir and tenofovir plus lamivudine), based on expert opinion. The model considers up to three treatments in sequence followed by BSC, and a total of 262 strategies are considered.

The model is reported to be based on previous models of antiviral agents in the treatment of chronic hepatitis B and informed by expert opinion. The model has 17 disease states based on HBV DNA levels, compensated or decompensated cirrhosis, HCC, liver transplantation, and death, including duplicate states to allow for HBeAg-positive and HBeAg-negative patients (see Appendix 2). Patients are assumed to receive antiviral treatment in all these except HBsAg seroconverted and HBeAg seroconverted states (and death). Transitions between treatments and variation in the risk of drug resistance and the probability of HBeAg seroconversion and/or viral suppression are taken into account by replicating these 17 main disease states for

each of the 15 situations that represent the sequence of up to three treatments followed by BSC.

Direct comparative data for tenofovir exists only in first-line use as monotherapy against adefovir. A mixed treatment comparison (MTC) meta-analysis was conducted by the company to calculate the relative efficacy of the nucleos(t)ide treatments currently available in the UK, with lamivudine used as the reference agent. However, much of the data on resistance and that used to derive transition probabilities for combination treatment is taken from adefovir and lamivudine trials and has been applied to all combination treatments. In the absence of data, a wide range of assumptions have been made in relation to the transition probabilities and resistance rates. Resource use and costs are derived from a wide range of non-Welsh sources. As most other strategies were technically dominated by BSC, lamivudine followed by no treatment, and four strategies involving first-line use of tenofovir (i.e. other strategies would not be considered more cost effective than these strategies), lamivudine followed by no treatment is used as the strategy against which tenofovir strategies are compared. However, the extent to which this lamivudine strategy would actually be used in the practice in the patient population under consideration is uncertain, as lamivudine resistance develops in a high proportion of patients on monotherapy, and adefovir is an option is such patients.

The model has been provided to WMP and it is reported that (non-Welsh) UK expert clinicians have validated the model structure and key assumptions[3].

8.3.2 Population

The modelled cohort reflects patients meeting the licensed indication for tenofovir. The two key trials of tenofovir were conducted in patients with raised ALT and adequate renal function. In study 0102, patients (77% male) had a mean age of 44 years and were required to have active HBeAg-negative chronic hepatitis B infection, with HBeAg -negative and anti-HBeAg-positive at screening[10] while those in study 0103 (69% male) had a mean age of 34 years and were required to have active HBeAg-positive chronic hepatitis B infection[11]. However, the age and sex distribution of the modelled cohort, and the proportion of patients in each disease state, is based on a small audit of patients attending a hepatology clinic in London. The mean age of patients attending this clinic was 38.3 years (range 19-72 years) and 62.7% were male. It is reported in the company submission that the nurse specialist who provided the data from this audit felt that this clinic was broadly representative of other tertiary centres in the UK that do not perform liver transplant operations. However, the patients attending this clinic were predominantly of Chinese origin, which may not be typical of centres across the UK[3].

8.3.3 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A 40 year time horizon has been used in the base case analysis based on the finding that the "average" age of patients diagnosed with chronic hepatitis B is 38 years, most patients are male and Government Actuary Department data for Wales indicates that the life expectancy of a 38 year-old male is 40.2 years[3,14].

Each cycle length is one year and a half cycle correction has been applied so that patients are assumed to move between disease states halfway through each cycle.

8.3.4 Comparator

The interventions considered in the analysis comprised the nucleos(t)ides tenofovir, adefovir, entecavir, lamivudine and the most commonly-used combinations of these agents (adefovir plus lamivudine, entecavir plus adefovir and tenofovir plus

lamivudine), based on company-sought expert opinion. Of these combination therapy regimens, adefovir plus lamivudine is reported to be most commonly used at present[3].

Interferon-alpha and peginterferon-alpha were not considered as comparators as interferons are generally given early in the treatment pathway to a different subgroup of patients, and at this time, it is felt unlikely that use of tenofovir would replace use of interferon and peginterferon in Welsh clinical practice. Telbivudine was not considered in the analysis as it was considered to be rarely used in the UK. Although there is a small amount of evidence supporting off-label use of other treatments such as emtricitabine or emtricitabine plus tenofovir in chronic hepatitis B , the experts interviewed by the company are reported to have suggested that HBV mono-infected patients rarely receive unlicensed or off-label treatments other than tenofovir[1]. The efficacy data of combinations for which there are no RCT data are based on the assumptions described in Section 8.3.5.1.

All logically-plausible combinations of up to three treatments in sequence were considered in the analysis. BSC was included at the end of each treatment pathway as a fixed fourth-line treatment to which patients cannot become resistant. A total of 262 strategies (accounting for all the various treatment pathways and sequences mentioned) are considered in the analysis.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

Efficacy data in the model relate to the probability of transitioning between the different disease states, which varies depending on the strategies selected and the development of drug resistance.

Direct comparative data for tenofovir exists only against adefovir, as discussed in Section 6. An MTC meta-analysis was therefore conducted by the company to calculate the relative efficacy of the nucleos(t)ide treatments currently available in the UK, with lamivudine used as the reference agent. Trials identified in a systematic review were used to provide data on HBeAg loss, HBeAg seroconversion and on the number of patients with HBV DNA levels below all thresholds reported (up to a maximum of 1,000 copies/ml), and specifically the proportion of patients with HBV DNA <300 copies/ml (which in the model represents viral suppression to the point of being undetectable). In those trials not providing direct data on the proportion of patients achieving HBeAg seroconversion or on the proportion of patients achieving the threshold of <300 copies/ml, data has been imputed as outlined in Appendix 2[3]. The main results of the MTC provide the proportion of patients achieving HBeAg seroconversion and the proportion achieving viral suppression (and, conversely, active disease) at the end of one year so that transition probabilities could be derived for each treatment and placebo for a range of sub groups of patients:

HBeAg-positive nucleos(t)ide-naïve HBV mono-infected patients
HBeAg-positive lamivudine-resistant mono-infected patients
HBeAg-positive and HBeAg-negative nucleos(t)ide-naïve HBV mono-infected patients
HBeAg-positive lamivudine-resistant patients with or without HIV co-infection
HBeAg-positive and HBeAg-negative lamivudine-resistant patients with or without HIV co-infection

Due to a lack of data, MTC analyses were not possible for the subgroups of HBeAg-negative nucleos(t)ide-naïve patients and HBeAg-negative lamivudine-resistant patients. Therefore, post-hoc analyses on HBV DNA were conducted that combined available trials on HBeAg-negative patients and those on HBeAg-positive patients together into a single analysis and considered the proportion of patients who were

HBeAg-positive at baseline as a covariate. The values obtained were used to generate transition probabilities for HBeAg-negative states[3].

The MTC meta-analyses, and the analysis that combined data on HBeAg-positive and HBeAg-negative nucleos(t)ide-naïve patients together, indicated that tenofovir is the most effective nucleos(t)ide treatment evaluated in RCTs in terms of achieving undetectable HBV DNA (<300 copies/mL) at one year. Tenofovir was reportedly associated with the highest probability of achieving undetectable HBV DNA in lamivudine-resistant patients, but the tenofovir data presented in the company submission for lamivudine-resistant patients appears to relate only to those patients who are co-infected with HIV. There were reportedly no statistically significant differences between the other nucleos(t)ides in these patients. There were also no statistically significant differences between nucleos(t)ides in terms of HBeAg seroconversion, either in treatment-naïve or lamivudine-resistant patients. Results of the MTC are tabulated in Appendix 2.

A number of assumptions are used in the calculation of the relevant transition probabilities. In cases where two nucleos(t)ides were used in combination, it was assumed that the efficacy of the combination was equal to that of the most effective component of that combination. This assumption was reportedly validated in an expert interview, but it may mean that the benefits of combination therapy are underestimated. It was also assumed that nucleos(t)ide treatment has no impact on the probability of HBsAg seroconversion but relatively few of the trials meeting the inclusion criteria for the meta-analysis reported data on HBsAg seroconversion. Therefore it is uncertain how reliable this assumption is. Due to a lack of data, the probability of HBeAg seroconversion in lamivudine-resistant patients receiving adefovir or tenofovir was assumed to be equal to the probability of HBeAg seroconversion in treatment-naïve patients. For a number of different transitions that may be influenced by treatment (e.g. those associated with the risk of disease progression in patients with severe liver disease, such as the probability of moving between decompensated and compensated cirrhosis and the probability of dying from the decompensated cirrhosis, liver transplant and post-liver transplant states), data were only available for adefovir or lamivudine. In these cases, all treated patients were assumed to have the same probability of improvement/progression regardless of which nucleos(t)ide they were receiving. In addition, it was assumed that nucleos(t)ide therapy would have no impact on mortality associated with HCC or that associated with compensated cirrhosis as most studies evaluating nucleos(t)ides in patients with compensated cirrhosis did not report mortality. Company-sought expert opinion suggested that this assumption is likely to be conservative[3].

Treatment resistance is defined for the purposes of the model as the appearance of conserved site changes or mutations known to be associated with drug resistance AND a ≥1 $\log_{10}$ copies/ml increase in HBV DNA from nadir or the reappearance of HBV DNA levels detectable by PCR in cases when they had been undetectable while on treatment[3]. The probabilities of developing resistance used in the model are based on pooled analyses of resistance data for lamivudine, entecavir, adefovir and tenofovir. The pooled annual risk of resistance was calculated by adding up the total number of patients becoming resistant in any given year and the total number of patients monitored in that year. Pooled analyses were conducted separately for combination therapy, for monotherapy and for patients who were lamivudine-resistant at baseline.

For tenofovir and for combination therapy, there were relatively few long-term studies that included more than 100 patients. No cases of virologic resistance to tenofovir have been observed in any population and zero cell counts were also observed in some years for other treatments, such as adefovir plus lamivudine in treatment-naive

patients. However, experience with older nucleos(t)ides suggests that it is likely that some cases of drug resistance will eventually be observed. In those cases where no resistance was observed, one hypothetical patient who was assumed to have developed resistance was added to the sample. Where resistance data were unavailable for combination therapy in treatment-naive patients, it was assumed that the risk of resistance would be ten percent of the risk of resistance associated with the component of the combination therapy that had the highest risk of resistance. This assumption was stated in the company submission to be based on data from a small number of nucleos(t)ide-naive patients who received adefovir plus lamivudine in an RCT, of whom two percent (1/49) developed breakthrough of a mutant HBV compared with 20% (10/49) who were receiving lamivudine monotherapy[15]. The company submission reports a relative risk of 0.10 for this outcome and a 95% confidence interval (CI) of 0.01 to 0.75[3]. Given the wide CI, small number of patients and the fact that lamivudine monotherapy is potentially more prone to result in resistance than some other agents, the use of the point estimate of the relative risk of 0.10 would seem to be subject to some uncertainty.

The results of the pooled analysis were applied within the economic model for all years in which at least 20 patients were treated and monitored for resistance. In cases where fewer than 20 patients have been monitored in any given year of therapy, the resistance rates in that year were based on the rates observed in the previous year. The resistance rate applied to year five and all subsequent years was the weighted average of the values for each year (weighted by the number of patients monitored for that period of time)[3]. It is uncertain how reliable this approach is, as the probability of resistance developing would be expected to increase over time.

Based on the above assumptions, the company has provided a breakdown of the estimated treatment durations as generated by the model. First-line treatment with tenofovir monotherapy is estimated to last 14.79 years, and 13.81 years with entecavir, 10.17 years with adefovir, 3.29 years and with lamivudine monotherapy. BSC treatment duration is estimated at 11.58 years. First-line treatment with tenofovir and lamivudine in combination is estimated to last 10.99 years, which is less than tenofovir monotherapy due the assumptions in the model regarding development of resistance in the absence of direct data (see 8.3.8.1).

8.3.5.2 Adverse events

The model does not consider adverse events, either from a cost or disutility perspective. This is stated in the company submission to be because all nucleos(t)ides are well tolerated and the incidence of various side effects occurs at a similar low rate, with most having no impact on quality of life[3]. In study 0102, the frequency of drug-related adverse events and serious adverse events was comparable between groups[10]. In study 0103, the incidence of drug-related adverse events was higher with tenofovir (30.7%) versus adefovir (16.7%), p=0.018[11]. Gastrointestinal disorders were more frequently reported in the tenofovir group (13.6% versus 1.1%; p<0.01). However, these were mainly due to reports of mild nausea (see Section 6.2).

8.3.5.3 Utility weights

Utility values used in the model are based largely on those obtained using a standard gamble approach in 93 chronic hepatitis B patients in the UK in 2005[16]. Six health states (active chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, HCC, first year following liver transplant and subsequent years following liver transplant) were defined using the Liver Disease Quality of Life Instrument and were then modified by a panel of three hepatologists. As few patients had severe disease (70% of the patients were pre-cirrhotic), the utilities derived were based on the health state descriptions. This study did not provide utilities for HBeAg or HBsAg

seroconversion, nor did it explore the relationship between viral load and quality of life[16]. Therefore, utility values for seroconverted patients were assumed to revert to those of age-matched population norms. The health state of HBeAg seroconverted was subsequently reduced by six percent, reportedly on the basis of a previous economic evaluation of interferon-alpha 2b for the treatment of patients with chronic hepatitis B infection who are positive for HBeAg, in which a panel of clinical experts felt that the presence of HBeAg and HBsAg would influence activities of daily living (such as sexual behaviour)[17]. However, it is not immediately clear why there should be a difference in this regard between patients who are HBeAg and HBsAg positive (and the value of six percent is not clear in the reference cited). For patients with viral suppression, it is assumed that the utility value will be the same as for those with active chronic hepatitis B (i.e. viral suppression is not associated with an improvement in quality of life in itself)[3].

8.3.6 Healthcare resource utilisation and cost

The healthcare resources and costs, other than the costs of nucleos(t)ide agents that are considered in the model are based on English and Scottish data/expert opinion. No Welsh-specific costs are included in the model and the company submission notes that variability exists in resource use between clinics, even within the same geographical regions[3]. However, sensitivity analyses suggest that variations in resource use and cost parameters had minimal influence on the model outputs.

8.3.6.1 Drug and administration costs

The licensed doses of nucleos(t)ides in the treatment of chronic hepatitis B are assumed in the model, and costs applied based on the prices listed in the British National Formulary.

8.3.6.2 Adverse event costs

Adverse events are not considered in the model.

8.3.6.3 Other resource use and costs

For the four least severe disease states (HBeAg seroconverted, HBsAg seroconverted, active chronic hepatitis B and viral suppression), resource use was based on expert opinion and estimates from a Health Technology Assessment (HTA) of adefovir and peginterferon alfa 2a in chronic hepatitis B[18]. Unit costs have been derived from published sources, or those included in the HTA that have been inflated to 2007 prices. The number of consultations that would typically be received each year by patients in different health states, during the first year of treatment and when resistance developed, and also what resources would typically be used in each consultation, were based on interviews conducted with two Scottish hepatologists. These clinicians agreed that most treated patients would attend clinic every three to six months. Liver biopsies and any additional tests required for diagnosis or assessment of whether treatment is suitable were assumed to have been conducted before entry to the model, regardless of whether nucleos(t)ide treatment will be given, so are not included. In addition to the resource use suggested by clinicians, all patients receiving adefovir or tenofovir were assumed to receive renal monitoring four times a year, as indicated in their SPCs[1,19].

For the more severe disease states (compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant and post-liver transplant), costs were based on large UK costing studies in hepatitis C, as the company submission states that audits recording actual healthcare resource use for individual patients were thought to give a more accurate estimate of the cost of managing these severe disease states than expert opinion[3]. It is assumed that the bulk of NHS costs for severe liver disease are associated with complications of liver disease rather than being specific to the virus causing the

disease, and this assumption was validated by expert interviews. The costs of managing compensated cirrhosis, decompensated cirrhosis and HCC were based on a large retrospective micro-costing study conducted as part of a HTA of treatment for mild hepatitis C, which was conducted at three UK centres (London, Newcastle and Southampton). The costs for liver transplantation and post-liver transplantation were taken from a similar large UK audit of patients undergoing liver transplantation for hepatitis C. The costs of hepatitis B immunoglobulin, which is not required in the management of patients with chronic hepatitis C, was added in to these costs based on information on dose and unit costs supplied by staff working at a Birmingham transplant centre[3].

8.3.7 Discounting

Costs and outcomes are discounted at 3.5%[3], which is the preferred discount rate. Rates of zero and six percent are explored in sensitivity analyses.

8.3.8 Results

8.3.8.1 Base case analysis – mixed cohort of patients

The base-case analysis generated results for 262 different treatment sequences in a mixed cohort of cirrhotic and non-cirrhotic HBeAg-positive and HBeAg-negative patients. It is only possible to discuss general themes of the overall results. Most strategies were technically dominated by the strategies of BSC, lamivudine followed by no treatment, and four strategies involving first-line use of tenofovir (i.e. most other strategies were more expensive and/or less effective and would not be considered cost effective compared with these strategies). Lamivudine followed by no treatment is therefore used as the strategy against which tenofovir strategies (and other strategies) are compared. However, the extent to which the strategy of lamivudine followed by no treatment would actually be used in the practice in the patient population under consideration in the model is uncertain. Lamivudine resistance develops in a high proportion of patients on monotherapy, and could limit the options for future treatment through cross-resistance to related drugs. A NICE technology appraisal of adefovir and peginterferon alfa 2a in patients with chronic hepatitis B[4], issued in 2006, noted that a strategy of treating chronic hepatitis B with lamivudine followed by adefovir for those in whom lamivudine-resistance developed reflected current practice at that time. It was also noted that there was a subgroup of people with highly replicative disease in whom resistance could develop rapidly, and in these people a strategy of using adefovir in combination with lamivudine might be appropriate[4].

Table 3 indicates the range of reported incremental costs per QALY for tenofovir and other nucleos(t)ides used as the first-line treatment compared with lamivudine followed by no further treatment. These results indicate that tenofovir monotherapy as the first-line treatment is associated with the lowest incremental costs per QALY (range £9,096 to £9,490) out of all the first-line strategies considered. The narrow range of incremental costs per QALY indicates that the choice of second- and third-line agents following first-line tenofovir has little influence on the model outputs. Furthermore, all strategies involving tenofovir monotherapy as the first-line treatment have lower incremental costs per QALY than all strategies involving tenofovir as a second-line agent (range £9,667 to £26,698). The lowest incremental costs per QALY for first-line tenofovir (tenofovir followed by lamivudine, followed by BSC; £9,096) and second-line tenofovir (lamivudine followed by tenofovir followed by BSC; £9,667) compared with lamivudine followed by no treatment are similar. However the incremental cost per QALY for the first-line use of tenofovir compared with second-line use of tenofovir is approximately £8,160. First-line use of tenofovir is more expensive (£46,982 versus £36,783) but is estimated to generate more QALYs (17.65 versus 16.40) than second-line tenofovir.

As adefovir plus lamivudine is the most commonly used combination of agents[3], and is noted in the NICE appraisal of adefovir as an appropriate option in those at risk of developing lamivudine resistance[4], table 3 also includes details of the combination of adefovir plus lamivudine for reference. The model predicts that all strategies involving tenofovir in combination with lamivudine as the first-line agent have lower incremental costs per QALY (£12,232 to £15,443) than all strategies involving first-line adefovir plus lamivudine (range £20,575 to £25,504) when compared with lamivudine followed by no treatment. The use of tenofovir plus lamivudine as a first-line treatment is more expensive and is predicted to be less effective than the use of tenofovir monotherapy due to the assumptions employed around the development of resistance with lamivudine. The assumptions around transition probabilities and development of resistance with combination therapy, outlined in 6.1, should be considered when interpreting the results for combination therapy.

Table 3. Range of reported incremental costs per QALY for first-line strategies and second-line tenofovir strategies compared with a strategy of lamivudine followed by no treatment[3]

	Incremental cost per QALY range (£/QALY)	
	lowest	**highest**
First-line treatment in the strategy		
TDF monotherapy	9,096 (TDF – LAM – BSC)	9,490 (TDF – ADV+ENT – ADV+LAM)
TDF+LAM	12,232 (TDF+LAM – LAM – TDF)	15,443 (TDF+LAM – ENT+ADV – ENT)
ENT monotherapy	14,371 (ENT – LAM – TDF)	15,547 (ENT – ENT+ADV – ADV+LAM)
ADV monotherapy	15,409 (ADV – LAM – TDF)	20,736 (ADV – ENT+ADV – ENT)
ADV+LAM	20,575 (ADV+LAM – TDF – TDF+LAM)	25,504 (ADV+LAM – ENT+ADV – LAM)
Second-line treatment in the strategy		
TDF monotherapy or TDF+LAM	9,667 (LAM – TDF – BSC)	26,698 (ENT+ADV – TDF+LAM – BSC)

Key:
BSC, best supportive care; ADV, adefovir; ENT, entecavir; LAM, lamivudine; TDF, tenofovir;
(LAM+ADV – TDF – BSC), lamivudine plus adefovir as first-line strategy followed by tenofovir as second-line strategy followed by best supportive care as third-line strategy
NB: the incremental costs per QALY presented in the table are all relative to a strategy of lamivudine followed by no treatment. This table only gives an indication of the relative incremental costs per QALY ranges and it is not appropriate to compare the listed strategies in this table directly against each other

Many of the 262 strategies considered in the model, although considered plausible in company submission, would not be likely to be used in practice. For example, the lowest incremental cost per QALY associated with strategies using adefovir plus lamivudine as first-line treatment uses tenofovir as the second-line treatment and tenofovir plus lamivudine as the third-line treatment. This third-line treatment therefore contains two agents to which the patient may be resistant, so the likelihood of its use in practice should be low.

8.3.8.2 Sub-group analyses

Results of sub-group analyses are presented in which first-line use of tenofovir followed by second-line use of lamivudine (TDF – LAM) or second-line use of tenofovir following

first-line lamivudine (LAM – TDF) are compared with a strategy of lamivudine followed by no treatment (LAM – NT).

HBeAg-positive, non-cirrhotic chronic hepatitis B
TDF – LAM was associated with an incremental cost per QALY of £8,001.
LAM – TDF was associated with an incremental cost per QALY of £6,952.

HBeAg-negative, non-cirrhotic chronic hepatitis B
TDF – LAM was associated with an incremental cost per QALY of £9,623.
LAM – TDF was associated with an incremental cost per QALY of £10,940.

HBeAg-positive, compensated cirrhosis
TDF – LAM was associated with an incremental cost per QALY of £4,468.
LAM – TDF was associated with an incremental cost per QALY of £4,369.

HBeAg-negative, compensated cirrhosis
TDF – LAM was associated with an incremental cost per QALY of £10,597.
LAM – TDF was associated with an incremental cost per QALY of £10,496.

These sub-group analyses indicate that, compared with a strategy of LAM-NT, the incremental costs per QALY for first-line use and second-line use of tenofovir are very similar. In all sub-groups except non-cirrhotic patients with HBeAg-negative chronic hepatitis B, second-line use of tenofovir is associated with marginally lower incremental costs per QALY. However, the total discounted costs and the total discounted QALYs for first-line tenofovir treatment are both higher than for second-line tenofovir treatment in all sub-groups. At a willingness to pay that equals or exceeds each of the estimated incremental costs per QALY for first line tenofovir in the sub-groups above, first-line tenofovir will be a cost effective strategy (e.g. if the willingness to pay was £10,597 or more, then in all subgroups first-line tenofovir would be cost effective). The incremental costs per QALY for first-line tenofovir use compared directly against second-line tenofovir use (rather than against a strategy of LAM – NT) ranged from £4,629 to £10,773[3].

8.3.9 Sensitivity analysis

8.3.9.1 One way sensitivity analyses

One-way sensitivity analyses have been conducted around TDF – LAM versus LAM – NT, LAM – TDF versus LAM – NT, and TDF – LAM versus LAM – TDF. In each case, the model is most sensitive to the assumed probability that patients who are HBeAg-negative will develop cirrhosis. In the base case analysis, this probability is nine percent. Threshold analysis indicates that the incremental cost per QALY increases to over £20,000 when the probability is reduced to 0.67% in the TDF – LAM versus LAM – NT analysis and 0.80% in the LAM – TDF versus LAM – NT analysis.

The model was also sensitive to the probability of HBeAg seroconversion and viral suppression for tenofovir-treated patients, and the assumptions of excess mortality associated with viral suppression. However, it is suggested that no logically plausible value for any of the parameters tested could result in the incremental cost per QALY for tenofovir to exceed £30,000 and the tornado diagrams generated for each strategy comparison all indicate incremental costs per QALY estimates below £20,000. Threshold analysis on the time horizon of the analysis suggests that the incremental cost per QALY would reach £20,000 using a time horizon of 18 years, and £30,000 using a time horizon of 13 years. The base case analysis uses a time horizon of 40 years on the basis that this is close to the population norm life expectancy of patients making up the modelled cohort, who are diagnosed with chronic hepatitis B at age 38 years. The company submission suggests that tenofovir may therefore not be cost

effective (at a willingness to pay of £30,000 per QALY gained) in patients with a life expectancy of less than 13 years.

8.3.9.2 Additional scenario analyses

A wide range of analyses have been conducted by varying parameter values in the model. Most are reported to have little influence on the model outputs. The exceptions are analyses conducted using time horizons in the range of 5 to 60 years (as discussed above), and the first-line use of tenofovir in patients with decompensated cirrhosis (outside the current licensed indications). The incremental costs per QALY for TDF – LAM versus LAM – NT and LAM – TDF versus LAM – NT were reported as £23,192 and £17,999, respectively. For TDF – LAM versus LAM – TDF, the incremental cost per QALY was reported as £72,308. However, the company submission notes that these analyses should be interpreted with caution due to the fact that the data for tenofovir in decompensated patients are based on trials of adefovir and lamivudine.

8.3.9.3 Probabilistic sensitivity analysis

Ten scenarios were considered in probabilistic sensitivity analyses (PSA), for which 5,000 simulations were run for each. All parameters other than unit costs were varied simultaneously by sampling from appropriate distributions fitted around the transition probabilities, utility values, relative risks and (non-unit) costs and quantities of resource use.

All cost- effectiveness ratios were slightly higher than those estimated in the deterministic base case analysis, e.g. the incremental cost per QALY for TDF – LAM versus LAM – NT was estimated as £10,668 (95% CI 6,782 to 25,424) in the PSA compared with £9,096. First-line tenofovir was still the most cost-effective strategy. Cost-effectiveness acceptability curves indicate that, compared with LAM – NT, the probability of first-line tenofovir being cost effective at a willingness to pay (WTP) threshold of £20,000 per QALY is around 95%, and at £30,000 is around 98%. Compared with second-line tenofovir, the probability of first-line tenofovir being cost effective at a WTP of £20,000 per QALY is around 92%, and at £30,000 is around 97%.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

The company submission describes a budget impact analysis based on UK prevalence and incidence data, confidential data on file on current market share and prescribing volumes of the available nucleos(t)ides, and a range of assumptions around uptake. As the majority of new diagnoses of chronic hepatitis B occur in immigrant populations, it is unclear how accurate the estimates of prevalence and incidence for Wales are. The budgetary impact estimates may be subject to some uncertainty.

8.4.2 Perspective and time horizon

The perspective of the analysis is that of NHS Wales over five years 2008 to 2012[3].

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

Department of Health data suggest a UK prevalence of chronic hepatitis B of 0.3%[20]. Applying this prevalence to the population of Wales would equate to around 8,800 patients with chronic hepatitis B. Incidence data are based on Health Protection Agency data for England and Wales, 1995-2000, which indicate a rate of 0.0074% per year[21]. This would be equivalent to around 220 new cases each year in Wales. However, it should be noted that the majority of new cases of chronic hepatitis B are in immigrant populations[21], which may differ in Wales from the UK as a whole.

From data used in the economic model, around 2.2% of patients are reported to have died in each of the first five years covered by the model, and 1.5% are reported to have seroconverted each year, which is assumed to be equivalent to resolving the infection. It is assumed that the population of Wales, mortality and incidence rates remain constant and a half life correction was applied such that incident cases had half the chance of dying as prevalent cases. On this basis, in 2008 the net number of patients with chronic hepatitis B is estimated to be 9,117. The number of prevalent cases is calculated to decrease each year (although the method of this estimation is unclear), such that by 2012 the net number of patients is estimated to be 8,687[3].

8.4.3.2 Rates of adoption

A large proportion of patients are estimated not to be receiving treatment.

For simplicity it has been assumed that the number of patients starting treatment each year is approximately ten percent of the number currently receiving therapy (although no justification is provided for this figure). Resistance data used in the economic model has been used to estimate the proportion of patients who develop resistance each year, based on a weighted average of resistance rates for each drug. On this basis it is estimated that 12.2% of patients currently receiving treatment would develop resistance each year and would be assumed to require second-line treatment in Wales each year. It has been assumed that, in practice, only 50% of these patients would actually start tenofovir treatment.

The company submission assumes that tenofovir may lead to the treatment of some patients who would not otherwise have received treatment with nucleos(t)ides. Therefore, sensitivity analysis has been conducted in an assumed extra 30 patients who would not otherwise have received treatment.

8.4.3.3 Costs and resource use

A weighted average cost of the current mix of nucleos(t)ide agents has been calculated, excluding the cost of telbivudine, which makes up a very small proportion of treatment in the UK. This weighted average cost is £7.54 per patient per day, or around £2,751 per patient per year. Tenofovir has a cost of £8.50 per patient per day, or around £3,103 per patient per year.

The additional costs of monitoring required with tenofovir and adefovir compared with other nucleos(t)ides are excluded on the basis that these are small and swamped by the drug costs.

8.4.4 Results

Assuming 50% uptake in the patients in Wales estimated to be eligible for treatment, the company submission indicates that the net budgetary impact of tenofovir would be £5,170 in 2008, rising to £25,852 in 2012.

8.4.5 Sensitivity analysis

Assuming 100% uptake in the patients in Wales estimated to be eligible for treatment, the company submission indicates that the net budgetary impact of tenofovir would be £10,341 in 2008, rising to £51,704 in 2012.

Assuming that 30 patients each year who otherwise would not receive treatment receive tenofovir, the budgetary impact, excluding those patients above, would be £93,075 in 2008, rising to £465,375 in 2012.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Treatment with tenofovir should be initiated only by healthcare professions experienced in the management of viral hepatitis; however continued care may be suitable for provision under shared care arrangements.

9.2 Related advice:

- United Kingdom National Guideline on the management of the Viral Hepatitides A, B & C (2005)[7]
- British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2008)[22]

Previous AWMSG/NICE advice:

All Wales Medicines Strategy Group (AWMSG):

- Truvada® (emtricitabine and tenofovir) was recommended for use by AWMSG in antiretroviral combination therapy for the treatment of HIV-1 infected adults on 12th June 2007.

NICE:

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. Technology appraisal (TA96) advice issued February 2006[4].
- Entecavir for the treatment of chronic hepatitis B. Single Technology Appraisal expected date of issue August 2008 (14th wave).
- Telbivudine for the treatment of chronic hepatitis B. Single Technology Appraisal expected date of issue August 2008 (14th wave).
- Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B. Single Technology Appraisal advice due 2009 (17th wave).

9.4 Ongoing studies

- Follow-up data to study 0102 and 0103 are anticipated.
- Study 0106 and 0108: see Appendix 1, table 3

9.5 Patient organisation information

A patient organisation submission by the Hepatitis B Foundation was provided to AWMSG members.

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APPENDIX 1. ADDITIONAL CLINICAL INFORMATION

Table 1: Primary efficacy response outcomes and components at Week 48 for Study 0102 (RAT analysis set) [3]

Reference	Study type	No of patients	Mean age (yr)	Patient Group	Treatment Regimen	Prior Treatment	Primary Outcome	Secondary Outcomes	Predictors of response
Monotherapy									
GS-US-174-0102	Phase III, randomised, double-blind, active control (to week 48) Open label extension phase ongoing (to week 240) US, Europe (incl. UK), Australia and New Zealand Week 48 data	375 received at least one dose (analysed group)	44	**HBeAg-negative** Baseline mean HBV DNA was 6.90 $\log_{10}$ copies/ml >60% baseline ALT >2xULN 64% Genotype D Baseline mean total Knodell score of 10.2 and fibrosis score of 2.3 19% cirrhotic 77% male	tenofovir (TDF) 300mg daily + placebo adefovir (ADV) (n=250) or ADV 10mg daily + placebo TDF (n=125)	66 (17.6%) lamivudine or emtricitabine 65 (17.3%) interferon	Proportion of patients who achieved a composite virological (HBV DNA <400 copies/ml) and histologic response at Week 48: TDF (70.8%) versus ADV (48.8%) (p<0.001)	Histologic response: 72.4% (TDF) and 68.8% (ADV), p=NS. HBV DNA <400 copies/ml: 94.4% (TDF) and 64.0% (ADV), p<0.001; <300 copies/ml: 92% (TDF) and 59.2% (ADV), p<0.001; <169 copies/ml: 91.2% (TDF) and 56% (ADV), p<0.001 ~77% of patients' ALT had normalised at week 48 in both groups. Mean change from baseline ALT at week 48 was -95.0U/L (TDF) and -124.4U/L (ADV), p=0.040 in favour of adefovir. Changes from baseline at conserved sites within HBV polymerase after 48 weeks: 7 (ADV) versus zero (TDF)	None identified

Table 2. Primary efficacy response outcomes and components at Week 48 of Study 0103 (RAT analysis set) [3]

Reference	Study type	No of patients	Mean age (yr)	Patient Group	Treatment Regimen	Prior Treatment	Primary Outcome	Secondary Outcomes	Predictors of response
Monotherapy									
GS-US-174-0103	Phase III, randomised, Double-blind, active control. Open label extension phases ongoing (to week 240) US & Europe (incl. UK), Australia and New Zealand Week 48 data.	242 (176 TDF, 90 ADV) completed the double-blind phase and were biopsied at week 48,	34	**HBeAg-positive** Baseline mean HBV DNA was 8.72 $\log_{10}$ copies/ml 77% baseline ALT >4xULN Most frequent genotype was D (33%) Baseline mean total Knodell score of 8.4 and fibrosis score of 2.4 20% cirrhotic 68.8% male	TDF 300mg daily or ADV 10mg daily	Lamivudine/ emtricitabine treatment-naïve (though later discovered 9 [3.4%] had previously received one or both 43 (16.2%) received interferon	Proportion of patients who achieved a composite virological (HBV DNA <400 copies/ml) and histologic response at Week 48: TDF (66.5%) versus adefovir ADV (12.2%) (p<0.001).	Histologic response 74.4% (TDF) and 67.8% (ADV), p=NS HBV DNA <400 copies/ml: 79.5% (TDF) 13.3% (ADV), p<0.001, <300 copies/ml: 74% (TDF) versus 12% (ADV), p<0.001 and <169 copies/ml: 69% (TDF) versus 9% (ADV), p<0.001. ALT had normalised at week 48 for 65% and 54% of patients receiving TDF and ADV respectively (difference estimate 13.6% [95%CI 1.1 to 26.1], p=0.032), HBeAg loss: 34/153 (22%) (TDF) versus 14/80 (18%) (ADV), p=0.018. 21% (TDF) and 18% (ADV) achieved seroconversion (p=NS) HBsAg loss: 3% versus 0% (p=0.018) HBsAg seroconversion: 1% versus 0% Changes from baseline at conserved sites within HBV polymerase after one year: 8 (ADV), 2 (TDF). Former not considered to be sign of drug resistance.	None identified

Table 3. Trials in development (combination)

Reference	Study type	Inclusion criteria	Treatment Regimen	Prior Treatment	Primary Outcome
0106	Phase II, randomised, double-blind, active control 48 and 96 week follow up US, Europe	DNA levels ≥1,000 copies/ml Serum ALT <10xULN Hepatitis C-, hepatitis D- and HIV-negative	Tenofovir 300mg + emtricitabine/tenofovir placebo or emtricitabine 200mg/ tenofovir 300mg + tenofovir placebo	Currently treated with adefovir for between 24 and 96 weeks.	HBV DNA <169 copies/ml at week 48
0108	Phase II randomised, double blind Multicentre	Decompensated liver disease Plasma HBV DNA ≥103 copies/ml CPT score of 7 to 12 ALT <10xULN Hepatitis C-, hepatitis D- and HIV-negative	Tenofovir 300mg + emtricitabine/tenofovir placebo + entecavir placebo or emtricitabine 200mg/ tenofovir 300mg + tenofovir placebo + entecavir placebo or entecavir 0.5mg or 1mg + tenofovir placebo + emtricitabine/tenofovir placebo	No prior entecavir or tenofovir <12 months prior adefovir	Proportion experiencing tolerability failure. Proportion with increased serum creatinine ≥0.5mg/dl from baseline or a confirmed serum phosphorus <2.0mg/dl

APPENDIX 2. Further information on the Health Economic evidence

A2.1 Outline of the model structure and cohort pathway

Ten disease states are considered in the basic model:

- HBsAg seroconverted
- HBeAg seroconverted
- Active CHB (HBV DNA ≥300 copies/mL)
- Viral suppression (HBV DNA <300 copies/mL)
- Compensated cirrhosis with detectable HBV DNA (HBV DNA ≥300 copies/mL)
- Compensated cirrhosis with undetectable HBV DNA (HBV DNA <300 copies/mL)
- Decompensated cirrhosis
- Liver transplant (year in which transplantation occurs)
- Post-liver transplant (≥9 months since transplantation)
- Hepatocellular carcinoma (HCC)
- Death

All states other than HBeAg seroconverted, HBsAg seroconverted, HCC and death were duplicated to allow for HBeAg-positive and HBeAg-negative patients. This produced a total of 17 disease states. An immunotolerant state, which represents the initial quiescent phase of CHB in patients who were infected at birth or early in life, was omitted from the model since this economic evaluation is concerned only those patients who had raised ALT at baseline.

Transitions between treatments and variation in the risk of drug resistance and the probability of HBeAg seroconversion and/or viral suppression were taken into account by replicating the 17 main disease states for each of the situations outlined below. There were therefore 15 copies of each of the main 17 states, to give a separate set of 17 states to cover each of the following situations:

- **Treatment 1:** this set of states covered the entire period for which patients are receiving Treatment 1 (the therapy designated the first-line option in that strategy). Since all patients considered in the model are suitable for treatment at baseline, all patients start to receive Treatment 1 at the very beginning of the model and time-variant transition probabilities and resistance rates can be applied and linked to the cycle. For example, the transition probabilities applicable to patients' first year of therapy were applied to Cycle 1, while the resistance rates and transition probabilities applicable to patients' second year of therapy were applied to Cycle 2.
- **Resistant to Treatment 1:** this set of states covered the year in which patients develop resistance to Treatment 1. The way in which state transitions, utilities and costs were applied to the year in which resistance occurred is described in Section 6.2.2.1 below. Patients were only permitted to stay in this state for one cycle, before progressing onto ‘Treatment 2, Cycle 1’ or ‘BSC’.
- **Treatment 2, Cycle 1:** this set of states represented the first year that patients spend on Treatment 2. Patients were only permitted to stay in this state for one cycle, before progressing onto ‘Treatment 2, Cycle 2’ or ‘Resistant to Treatment 2’.
- **Treatment 2, Cycle 2**
- **Treatment 2, Cycle 3**
- **Treatment 2, Cycle 4**
- **Treatment 2, Cycle 5 and subsequent years**
- **Resistant to Treatment 2**
- **Treatment 3 , Cycle 1**
- **Treatment 3 , Cycle 2**

- **Treatment 3 , Cycle 3**
- **Treatment 3 , Cycle 4**
- **Treatment 3 , Cycle 5 and subsequent years**
- **Resistant to Treatment 3**
- **BSC:** all patients who develop resistance to third-line treatment were assumed to continue to receive BSC with no antiviral therapy until death/seroconversion or for the remainder of the time horizon.

Patients were assumed to move from one set of states to another depending on the strategies selected and whether or not they developed drug resistance.

A2.2 Mixed Treatment Comparison meta-analyses

Imputation of proportion of patients with HBV DNA levels < 300 copies/ml

Data available from studies 0102 and 0103 were used to explore the statistical relationship between the proportion of patients with HBV DNA levels <300 copies/m1and other thresholds between 0 and 1,000 copies/ml. Based on the assumption that the proportion of patients below a threshold will increase by a constant percentage for every 100 copies/ml increase in the threshold used across all populations and all treatments, a logarithmic function was used to derive a predictive equation to convert the number of patients with HBV DNA below other thresholds into estimates of the number of patients with HBV DNA <300 copies/ml that could be used in the meta-analysis.

Imputation of proportion of patients with HBeAg seroconversion

Since patients cannot undergo HBeAg seroconversion without also losing HBeAg, it was assumed that a fixed proportion of patients who lose HBeAg will also have undergone HBeAg seroconversion and that this proportion will be the same for all treatments and all patient subgroups. This was reported to be the case in all studies (bar one which was excluded as an outlier), demonstrating that between 89% and 100% of patients who lose HBeAg also undergo HBeAg seroconversion. In cases where the incidence of HBeAg loss was reported without data on HBeAg seroconversion, it was therefore assumed that the number of patients with HBeAg seroconversion would be the average of the reported number who underwent HBeAg loss in the trials considered in the meta-analysis. This was 92.05% of cases.

Results of MTC meta-analyses – outcomes at one year

Treatment (No. trials)	HBV DNA <300 copies/mL		HBeAg seroconversion	
	% pts (95%CrI)	OR vs LAM (95% CrI)	% pts (95%CrI)	OR vs LAM (95% CrI)
HBeAg-positive nucleos(t)ide-naive HBV mono-infected patients				
Tenofovir (1)	93.7% (80.0%, 99.3%)[*,l,p]	52.78 (6.427, 226.4)	26.7% (11.1%, 49.1%)[p]	1.275 (0.441, 2.984)
Entecavir (3)	73.1% (57.6%, 87.6%)[l,p]	4.941 (2.228, 11.6)	23.9% (15.7%, 33.9%)[p]	1.027 (0.758, 1.361)
Telbivudine (3)	62.9% (44.8%, 81.7%)[l,p]	3.091 (1.275, 7.517)	25.7% (17.1%, 36.1%)[p]	1.132 (0.827, 1.51)
Telbivudine + lamivudine (1, n<60)	53.3% (21.9%, 84.3%)[p]	2.576 (0.434, 9.292)	13.5% (4.2%, 29.3%)	0.532 (0.15, 1.289)
Adefovir (4)	48.8% (25.8%, 77.5%)[p]	1.861 (0.551, 5.715)	22.1% (11.6%, 36.1%)[p]	0.946 (0.467, 1.703)
Lamivudine (9[‡])	38.4% (33.9%, 42.8%)[p]	-	23.5% (16.4%, 32.1%)[p]	-
Adefovir+ lamivudine (1, n<60)	37.5% (12.5%, 68.7%)[p]	1.182 (0.231, 3.651)	28.1% (13.2%, 47.6%)[p]	1.344 (0.536, 2.814)
Placebo (5[‡])	7.1% (1.5%, 18.5%)	0.129 (0.025, 0.373)	10.7% (5.6%, 17.7%)	0.393 (0.213, 0.65)
Nucleos(t)ide-naive HBV mono-infected patients – HBeAg-positive and negative combined				

Treatment (No. trials)	HBV DNA <300 copies/mL		HBeAg seroconversion	
	% pts (95%CrI)	OR vs LAM (95% CrI)	% pts (95%CrI)	OR vs LAM (95% CrI)
Tenofovir	94.65% (85.86%, 99.03%)	33.29 (6.876, 116.4)	-	-
Entecavir	79.04% (68.22%, 89.1%)	4.666 (2.464, 9.374)	-	-
Telbivudine	71.84% (58.64%, 84.76%)	3.161 (1.59, 6.505)	-	-
Telbivudine + lamivudine	61.63% (29.56%, 88.35%)	2.588 (0.461, 9.044)	-	-
Adefovir	62.17% (39.74%, 84.73%)	2.274 (0.744, 6.431)	-	-
Lamivudine	46.88% (43.2%, 50.43%)	-	-	-
Adefovir + lamivudine	45.39% (17.73%, 75.3%)	1.167 (0.246, 3.544)	-	-
Placebo	6.21% (1.37%, 15.26%)	0.077 (0.016, 0.207)	-	-
HBeAg-positive lamivudine-resistant/refractory HBV mono-infected patients				
Entecavir 1 mg	18.71% (3.14%, 43.22%)	20.98 (4.821, 69.66)	3.32% (0.34%, 10.33%)	2.432 (0.534, 6.983)
Entecavir 0.5 mg	18.37% (2.52%, 45.9%)	21.26 (3.669, 78.13)	3.25% (0.22%, 12.18%)	2.5 (0.282, 9.546)
Adefovir	27.21% (3.28%, 76.57%)	196.5 (1.579, 894)	33.1% (2.05%, 92.29%)	2336 (0.825, 3533)
Lamivudine	1.44% (0.23%, 3.55%)	-	1.58% (0.2%, 4.11%)	-
Adefovir + lamivudine	32.66% (9.24%, 73.25%)	206.1 (4.346, 872.4)	12.52% (1.51%, 45.95%)	97.61 (0.678, 270.4)
HBeAg-positive lamivudine-resistant/refractory HBV mono-infected and HIV co-infected patients				
Tenofovir	53.9% (7.28%, 96.73%)	1211 (4.4, 5853)	Analysis did not converge	
Entecavir 1 mg	20.01% (3.8%, 43.83%)	22.38 (5.002, 76.03)		
Entecavir 0.5 mg	19.5% (3.18%, 46.86%)	22.64 (3.766, 83.87)		
Adefovir	24.85% (3.3%, 71.56%)	111.3 (1.736, 668.2)		
Lamivudine	1.5% (0.25%, 3.75%)	-		
Adefovir + lamivudine	30.63% (8.86%, 70.35%)	127 (4.164, 729.1)		
Lamivudine-resistant/refractory HBV mono-infected and HIV co-infected patients – HBeAg-positive and negative combined				
Tenofovir	54.4% (15.7%, 90.4%)	349.9 (2.88, 2330)	-	-
Entecavir 1 mg	33.25% (0.75%, 87.82%)	22.77 (4.836, 77.77)	-	-
Entecavir 0.5 mg	32.48% (0.66%, 87.97%)	22.5 (3.895, 81.47)	-	-
Adefovir	21.05% (9.6%, 34.61%)	6.711 (217.202, 1.507)	-	-
Lamivudine	4.53% (0.06%, 22.87%)	-	-	-
Adefovir + lamivudine	41.41% (12.71%, 74.83%)	19.376 (534.759, 4.916)	-	-

CrI, credible (Bayesian probability) interval; OR, odds ratio; * significantly superior to all 7 treatments; [I] significantly superior to lamivudine; [P] significantly superior to placebo. † n<60. ‡ PCR unavailable for 3 placebo-controlled lamivudine trials. Significance declared at 0.05 level.