NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Tenofovir disoproxil for the treatment of chronic hepatitis B

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide the following information:

Further details of the literature search methodology and confirmation of the number of studies included in the systematic review; clarification of the population baseline characteristics of the studies in the mixed treatment comparison and whether critical appraisal of these studies was carried out; further justification of the choice of population mean age, use of particular resistance data and utility estimates in the economic model; further clarification of methods used to calculate mortality rates and the assumptions made about regression to cirrhosis in the economic model.

Licensed indication

Tenofovir disoproxil (Viread, Gilead) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This indication is based histological, virological, biochemical and serological responses mainly in adult nucleoside naïve patients with hepatitis B 'e' antigen (HBeAg) positive and HBeAg negative chronic hepatitis B with compensated liver function.

Background information on the course of the disease

Chronic hepatitis B infection is defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with HBV. HBV is transmitted by sexual contact, through the use of infected blood products and infected blood for transfusion, by reuse of contaminated needles and syringes, by vertical transmission from mother to child during or soon after birth, and by horizontal transmission among children. The risk of chronic hepatitis B depends on the nature of the immune response to the initial infection. This varies according to the age at which the infection is acquired. Almost all neonates, and about half of young children, develop a chronic infection if infected with HBV. In contrast, only about 2–10% of people who are infected as adults go on to develop chronic hepatitis B.

People with active chronic hepatitis B are at increased risk of liver cirrhosis (scarring of the liver tissue that may progress to liver failure) and primary liver cancer (hepatocellular carcinoma).

The diagnosis of chronic hepatitis B is based on the presence of well-characterised serological markers in the blood. HBV DNA is present in both acute and chronic hepatitis B. Hepatitis B surface antigen (HBsAg) is a viral protein detectable in the blood in both acute and chronic infection. Chronic hepatitis B is defined as persistence of HBsAg for 6 months or more after acute infection. Hepatitis B ‘e’ 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.

The natural history of chronic hepatitis B can be divided into phases, each of which may last many years.

- Immunotolerant phase. People who are infected at birth or in early childhood initially enter an ‘immunotolerant’ phase during which the immune system does not actively fight the virus. The virus replicates rapidly during this phase, but the person usually has no symptoms. The person is highly infectious, and may

infect other members of the family and community. This phase can last for many years before progressing to active disease.

- Active chronic hepatitis B. The first stage of active disease involves a period of increasing inflammatory hepatic necrosis as the immune system begins to fight the virus. This stage of the disease is characterised by elevated levels of viral DNA in the blood, persistently raised levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and evidence of hepatic necrosis and inflammation on biopsy. The liver damage caused by infection and inflammation may eventually lead to cirrhosis of the liver. Progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20%.
- HBeAg seroconversion. In people infected with an HBeAg-positive form of the virus, the next stage of the infection occurs when inflammation becomes sufficiently intense to cause lysis of infected hepatocytes. This produces a 'flare' of the disease with symptoms resembling acute hepatitis B, and leads to the development of antibodies against the 'e' antigen. This is referred to as 'HBeAg seroconversion'. The seroconverted disease state is associated with good quality of life and a relatively low risk of disease progression. It is referred to as the 'inactive HBsAg carrier state' because patients continue to express hepatitis B surface antigen (HBsAg). The spontaneous seroconversion rate is 5–10% per year, although this varies among populations. Once seroconversion has taken place, most people remain in the inactive HBsAg carrier state. However, increasing viraemia and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg negative strain of the virus.
- HBeAg negative chronic hepatitis B. In recent years a form of the virus that does not cause infected cells to secrete HBeAg has been discovered (sometimes called the 'precore mutant' strain). People can be infected with the so-called 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 of the virus. The prevalence of HBeAg-negative hepatitis varies geographically; it is more common in Asia and the Mediterranean region than in northern Europe. Chronic infection with HBeAg-

negative HBV 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 chronic infection with HBeAg-negative HBV achieve a lasting remission. Progression to cirrhosis of the liver has been estimated to occur in 8–10% of people with HBeAg-negative chronic hepatitis B each year.

- HBsAg seroconversion. The development of antibodies against HBsAg, with clearance of HBsAg, occurs spontaneously in about 0.5–2% of people with chronic hepatitis B each year in western countries. In countries where hepatitis B is endemic, the rate is much lower – between 0.05 and 0.08% per year. Clearance of HBsAg is most likely to occur in the year following HBeAg seroconversion. It signifies resolution of the chronic infection. Variants of HBV (known as 'occult hepatitis B') that are not associated with detectable HBsAg by current immunoassays have been recognised.

The aim of treatment is to prevent progression to cirrhosis or hepatocellular carcinoma. Treatment may be given as a finite course (circumscribed therapy) – with the intention of allowing the immune system to respond and control the infection without the need for further drug treatment – or as long-term viral suppressive therapy. Long-term therapy is needed if short-term therapy is unsuccessful.

Key issues for consideration

Clinical effectiveness

- Which of the various surrogate markers of response to treatment used in the manufacturer's submission best reflect long-term outcomes in chronic hepatitis B?
- What is the Committee's view on the most appropriate place for tenofovir disoproxil in the pathway of care?
- What is the Committee's view of the potential for viral resistance with tenofovir disoproxil in the treatment of CHB?

Cost effectiveness

- What is the committee's view on the plausibility of the efficacy estimates for tenofovir dipivoxil in HBeAg-negative disease used in the model?
- What is the Committee's view on the plausibility of the resistance probabilities used in the model?
- Taking into account the exploratory analyses and corrections of the ERG, is the Committee satisfied that the estimates of the incremental cost-effectiveness of tenofovir disoproxil are robust?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Table 1 Decision problem in the manufacturer's submission

Population	Adults with active chronic hepatitis B (evidence of viral replication and active liver inflammation) and compensated liver disease. HBeAg-positive and HBeAg-negative disease will be considered separately.
Intervention	Tenofovir disoproxil fumarate alone. Secondary analyses of combination therapy regimens that may be considered clinically appropriate have been included for completeness.
Comparators	Lamivudine. Adefovir dipivoxil. Entecavir. Secondary analyses of combination therapy regimens comprising the above agents that may be considered clinically appropriate have been included for completeness. However neither interferon alfa-2a/2b nor peginterferon alfa-2a will be considered in the analysis because they are generally given as initial treatment to a selected group of patients.
Outcomes	The outcome measures to be considered include: • HBeAg seroconversion rate • HBsAg seroconversion rate • virological response (HBV DNA) • histological improvement (inflammation and fibrosis) • biochemical response (such as, ALT levels) • time to treatment failure • survival • adverse effects of treatment • health-related quality of life.
Economic evaluation	The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY gained.

1.2 Evidence Review Group comments

1.2.1 Population

The Evidence Review Group (ERG) judged that the population specified matched that in the appraisal scope and the licensed indication, and is appropriate for the NHS. However the ERG pointed out the manufacturer's submission included some studies containing people co-infected with HIV, which was not in accordance with the scope and decision problem.

1.2.2 Intervention

The ERG concluded that the description of the intervention in the decision problem reflected the marketing authorisation and current UK clinical practice, and was appropriate for the NHS.

1.2.3 Comparators

The ERG pointed out that interferon alfa-2a/2b and peginterferon alfa-2a were not included in the decision problem. The ERG concluded that the manufacturer's justification for excluding them was acceptable (that is, they are generally appropriate for a smaller group of selected patients).

The ERG noted that telbivudine was included as a comparator in the mixed treatment comparison (but not in the economic model). It accepted the manufacturer's justification that including randomised controlled trials (RCTs) of telbivudine facilitates the network of evidence needed to build a mixed treatment comparison.

1.2.4 Outcomes

The ERG judged that the outcomes listed in the decision problem reflect those in the scope of the appraisal and all meaningful clinical outcomes have been included. However, the ERG pointed out that time to treatment failure, survival and health-related quality of life were not reported from the included RCTs.

1.2.5 Economic evaluation

The ERG concluded that the manufacturer's approach to economic modelling was reasonable, but the methods used to identify, select and critically appraise studies contributing data to key input parameters in the model were inadequate.

1.3 Current NICE recommendations

'Telbivudine for the treatment of chronic hepatitis B' NICE technology appraisal guidance 154 (2008).

- Telbivudine is not recommended for people with chronic hepatitis B.

'Entecavir for the treatment of chronic hepatitis B' NICE technology appraisal guidance 153 (2008).

- Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

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

- Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg positive or HBeAg negative), within its licensed indications.
- Adefovir dipivoxil is recommended as an option for the treatment of adults with chronic hepatitis B (HBeAg positive or HBeAg negative) within its licensed indications if:
  - •treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
  - a relapse occurs after successful initial treatment, or
  - treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.

- Adefovir dipivoxil should not normally be given before treatment with lamivudine. It may be used either alone or in combination with lamivudine when:
  - treatment with lamivudine has resulted in viral resistance, or
  - lamivudine resistance is likely to occur rapidly (for example, in the presence of highly replicative hepatitis B disease), and development of lamivudine resistance is likely to have an adverse outcome (for example, if a flare of the infection is likely to precipitate decompensated liver disease).

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's proposed place for tenofovir disoproxil in the pathway of care.

2.1.1 Clinical effectiveness evidence

The manufacturer identified seven RCTs comparing tenofovir disoproxil with adefovir dipivoxil, emtricitabine/tenofovir disoproxil, lamivudine or placebo, three of which met the criteria for inclusion in the review.

Two of these studies were head-to-head RCTs comparing tenofovir disoproxil monotherapy with adefovir dipivoxil monotherapy in nucleoside analogue-naive populations. One study was in HBeAg-positive chronic hepatitis B and the other was in HBeAg-negative chronic hepatitis B. Both studies were multinational double-blind RCTs, conducted in the USA and a number of EU countries; neither had been published in peer-reviewed journals.

Table 2 gives details of the main results of these two RCTs. Tenofovir disoproxil gave a greater proportion of complete responses (histological response and HBV DNA below 400 copies/ml) than adefovir dipivoxil in people with HBeAg-positive and HBeAg-negative disease at 48 weeks. The difference was statistically significant.

In the study in HBeAg-positive disease, a similar proportion of people with HBeAg-positive disease had seroconversion or HBeAg loss with tenofovir disoproxil and adefovir dipivoxil, but there was statistically significantly more

hepatitis B surface antigen (HBsAg) loss with tenofovir disoproxil at 48 weeks: 3.2% (5/158) versus none (0/82) (p=0.018). In the study in HBeAg-negative disease, subjects in either treatment group experienced HBsAg loss or seroconverted to anti-HBs by Week 48.

Both RCTs reported a lower proportion of people with potential future resistance (HBV mutation-conserved site changes) with tenofovir disoproxil than with adefovir dipivoxil at 48 weeks. There were no cases of substitution of the HBV polymerase/reverse transcriptase associated with resistance to tenofovir disoproxil in either study.

A subgroup analysis using data from both trials among people with liver cirrhosis (59% had HBeAg-negative disease) found tenofovir disoproxil monotherapy resulted in a statistically significantly greater proportion of people with HBV DNA below 400 copies/ml than adefovir dipivoxil alone. Clinical study reports for two of the trials state that no subgroup analyses were planned, therefore it cannot be assumed that this was a pre-specified analysis.

A subgroup analysis using data from both trials among people who had previously received more than 12 weeks of treatment with lamivudine (87% were HBeAg negative) found that similar proportions of lamivudine-treated and lamivudine-naive participants had HBV DNA below 400 copies/ml.

The manufacturer identified one head-to-head trial that compared tenofovir disoproxil alone and tenofovir disoproxil in combination with emtricitabine (Truvada, Gilead) in a mixed population of nucleoside-naive and lamivudine-treated people with HBeAg-positive and -negative disease. This study was a multinational double-blind RCT conducted in the USA and a number of EU countries. There was no statistically significant difference in the proportion of people with HBV DNA below 400 copies/ml between the two treatment groups at 48 weeks (81.1% for tenofovir alone versus 80.8% for the combination; p = 0.988).

Table 2 Results of the two included randomised controlled trials at 48 weeks – comparisons of tenofovir disproxil fumarate (TDF) and adefovir dipivoxil (AD)

Study no.	Population	N	Virological response 1		Histological response 2		Complete response3	
			TDF v AD % (p value)	Absolute difference (percentage points)* TDF – AD (95% CI)	TDF v AD % (p value)	Absolute difference (percentage points) TDF – AD (95% CI)	TDF v AD % (p value)	Absolute difference (percentage points) TDF – AD (95% CI)
102	Nucleoside-analogue-naive, HBeAg-negative	323	94.4 v 64.0 (<0.001)	30.3 (21.6 to 39.1)	72.4 v 68.8 (0.293)	5.2 (-4.5 to 14.9)	70.8 v 48.8 (< 0.001)	23.5 (13.2 to 33.8)
103	Nucleoside-analogue-naive, HBeAg-positive	266	79.5 v 13.3 (<0.001)	65.9 (56.8 to 75.0)	74.4 v 67.8 (0.320)	5.8 (-5.6 to 17.2)	66.5 v 12.2 (< 0.001)	54.1 (44.6 to 63.6)

TDF – tenofovir disproxil fumarate; AD – adefovir dipivoxil; 95%CI – 95% confidence interval; [1]Hepatitis B virus (HBV) DNA < 400 copies/ml; [2] ≥ 2 point decrease in the Knodell necroinflammatory score with no worsening of fibrosis (≥ 1 point increase in Knodell fibrosis score); [3] composite endpoint defined as histological response and HBV DNA below 400 copies/ml.

2.1.2 Mixed treatment comparison

The manufacturer pointed out that there were no trials that included all treatment options in any of the patient populations and therefore a series of mixed treatment comparison meta-analyses were carried out to assess the relative efficacy of adefovir dipivoxil, entecavir, lamivudine, telbivudine, tenofovir disoproxil and placebo in nucleoside-naïve and lamivudine-refractory patients. The included outcomes were HBeAg DNA suppression and HBeAg seroconversion, over a 1-year treatment duration. (See pages 59–60 of the manufacturer's submission for a description of methodologies used and pages 30–34 of the ERG report for critiques of this analysis.)

For HBeAg-positive disease, the mixed treatment comparison showed that tenofovir disoproxil has a statistically significantly higher predicted probability of HBV DNA response than all comparators, and a 98% probability that tenofovir disoproxil is the most potent [the manufacturer's term] nucleos(t)ide considered in the analysis in terms of suppression of HBV DNA. There was no statistically significant difference between nucleos(t)ides for the probability of seroconversion.

For HBeAg-negative disease, no meaningful analysis could be undertaken because of the small number of trials identified (see page 63 of the manufacturer's submission for further details). The manufacturer undertook an additional analysis combining trials on HBeAg-positive and HBeAg-negative disease in which the proportion of patients who were HBeAg-positive was considered as a covariate. The results were similar to the HBeAg-positive subgroup. (See table 4 for further details.)

Five RCTs in HBeAg-positive lamivudine-refractory HBV mono-infected patients were identified, none of which were trials of tenofovir disoproxil. The results of the mixed treatment comparison found that all treatments significantly increased the chance of achieving undetectable HBV DNA relative to lamivudine, although there were no statistically significant differences between other nucleos(t)ides. (See pages 63–4 of the manufacturer's submission for further details.)

Tables 3 and 4 contain details of the data used and the results of the mixed treatment comparison for HBeAg negative disease (taken from the manufacturer's submission Appendix 4, pages 42 and 46)

Table 3: Data used in the meta-analysis of treatment-naïve HBeAg-negative disease

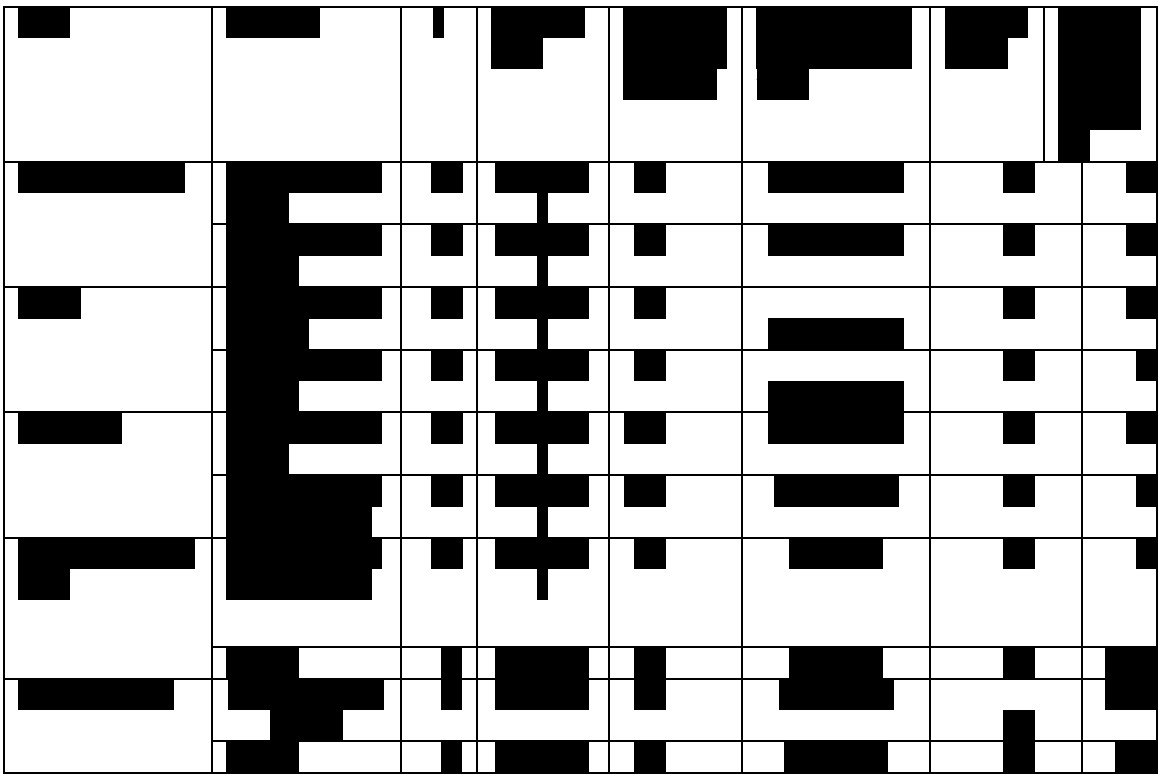

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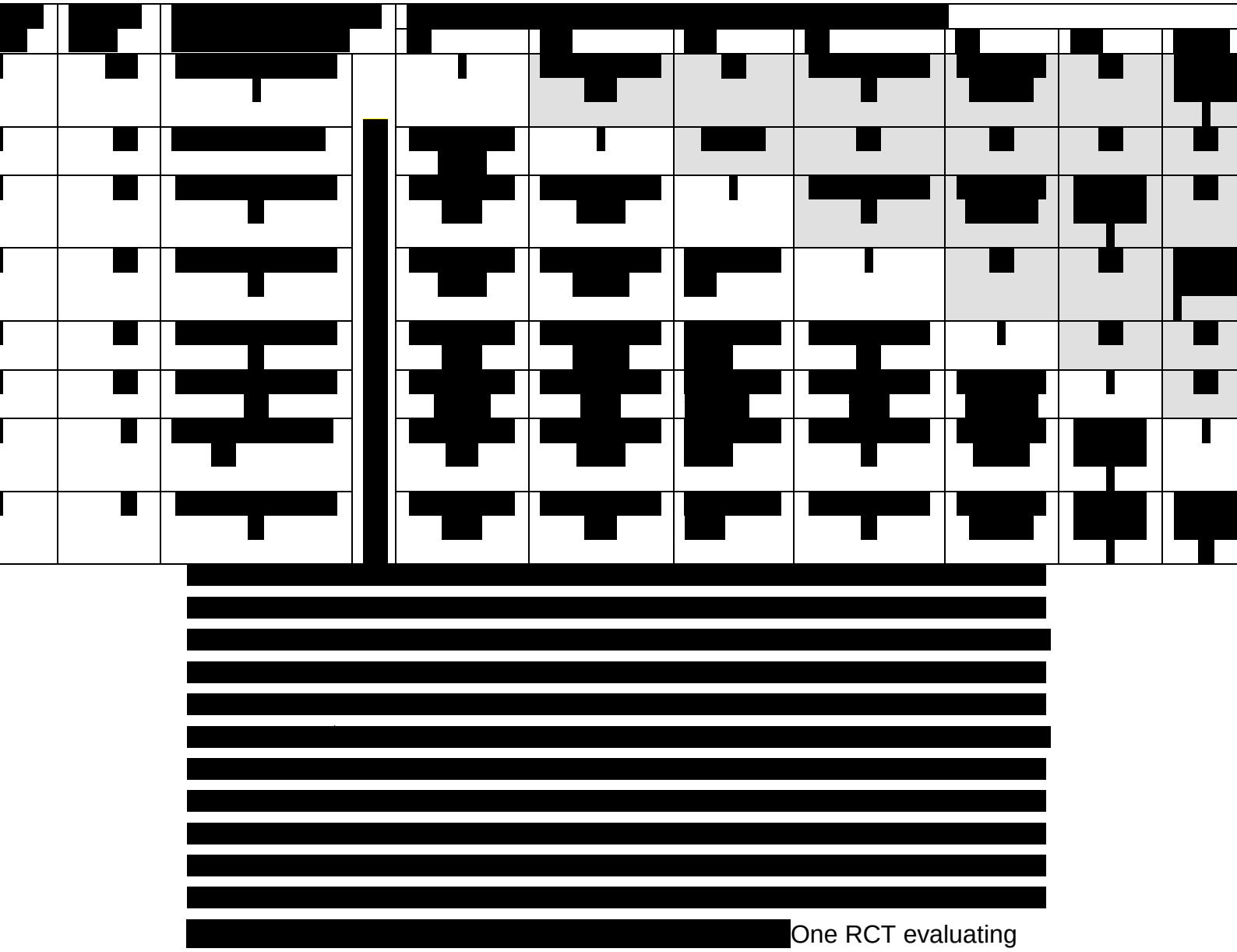
Table 4 Summary of results of the MTC for the HBeAg-negative populations (data from HBeAg-positive and negative populations combined) HBV DNA <300 copies/ml at year one .



One RCT evaluating tenofovir disoproxil in HBeAg-negative lamivudine-refractory HBV mono-infected populations was identified The manufacturer undertook an analysis that considered the results of trials of tenofovir disoproxil in HBV mono-infected and HIV co-infected HBeAg-positive and -negative populations. This analysis showed that tenofovir has the highest chance of achieving undetectable HBV DNA. The ERG did not consider this analysis because HIV co-infected populations were included.

2.1.3 Adverse events

Data on adverse advents in the manufacturer's submission came from the two head-to-head trials of tenofovir disoproxil monotherapy compared with adefovir dipivoxil monotherapy at 48 weeks. Incidence of grade three to four adverse events, as well as serious adverse events, were similar between treatment groups, with no reported deaths in either study. However, statistically significantly more participants did have at least one treatment-related adverse event in the tenofovir disoproxil treatment group one study. The incidence of arthralgia was statistically significantly higher for the tenofovir disoproxil treatment group in another study (for further details see pages 65 to 70 of the manufacturer's submission).

2.1.4 Resistance

There were no cases of mutation or resistance in the three head-to-head trials of tenofovir disoproxil and adefovir dipivoxil monotherapy. Meta-analyses were undertaken by the manufacturer to compare rates of resistance between available treatments, using data from the above three RCTs and observational studies identified while undertaking the systematic review (manufacturer's submission appendix 5, page 58).

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. Studies that formed part of published pooled analyses that were included in the review, and those believed to overlap with other studies, were excluded from weighted averages. Pooled analyses were conducted separately for combination therapy, for monotherapy and for patients who were lamivudine resistant at baseline.

The results for treatment-naïve and lamivudine-refractory patients at 1 year and 5 years are presented in tables 6 and 7.

Table 5 Risk of resistance at 1 and 5 years for people with treatment-naïve chronic hepatitis B (manufacturer's submission appendix 5 pg 67)

		Resistance at 1 year		Resistance at 5 years	
Intervention	**N pooled studies**	**Mean % (SE)**	**95% CI**	**Mean % (SE)**	**95 % CI**
Tenofovir disoproxil	2	[redacted]	[redacted]	[redacted]	[redacted]
Adefovir dipivoxil	6	0.26 (0.15)	0.00 to 0.54	3.13 (2.17)	0.00 to 7.39
Lamivudine	9	19.21 (0.73)	17.78 to 20.64	22.46 (0.77)	20.95 to 23.97
Entecavir	N/A *	0.36 (0.25)	0.00 to 0.85	0.83 (0.83)	0.00 to 2.46

* Year 1 calculated from US prescribing information, year 5 calculated from percentages given by Colonno et al 2007.

Table 6 Risk of resistance at 1 and 5 years for people with lamivudine resistant chronic hepatitis B (manufacturer's submission appendix 5 pg 67)

		Resistance at 1 year		Resistance at 5 years	
Intervention	**N pooled studies**	**Mean % (SE)**	**95% CI**	**Mean % (SE)**	**95 % CI**
Tenofovir disoproxil	1	0.76 (0.76)	0.00 to 2.25	1.57 (1.09)	0.00 to 3.71
Adefovir dipivoxil + lamivudine	7	3.87 (1.16)	1.60 to 6.14	3.87 (1.16)	1.60 to 6.14
Entecavir	1	1.07 (0.75)	0.00 to 2.54	15.09 (4.92)	5.46 to 24.73

2.2 Evidence Review Group comments

The ERG viewed the manufacturer's search strategy as limited because key databases were not searched and the search was not up to date However, the ERG did not believe any key trials were missing from the submission. The ERG said the manufacturer's quality assessment of the RCTs was appropriate and used the NICE criteria (for further details see pages 24–29 of the ERG report).

The ERG pointed out that the manufacturer based the assessment of clinical effectiveness on three RCTs. The ERG viewed the two trials that compared tenofovir disoproxil with adefovir dipivoxil as being methodologically sound and measuring clinically relevant outcomes. However, the comparison of tenofovir disoproxil with tenofovir disoproxil plus emtricitabine was beyond the scope of the appraisal and therefore was not considered relevant by the ERG.

The ERG viewed the mixed treatment comparison methodology as generally sound, but pointed out that it was weakened by the small number of studies and single studies in some networks, a lack of quality assessment of included studies, no discussion of potential clinical heterogeneity and limited discussion of statistical heterogeneity. Therefore the ERG concluded that the results should be treated with caution.

The ERG viewed the pooled analysis of resistance in the manufacturer's submission as appropriate, but pointed out that data for long-term resistance are currently unavailable.

2.3 Statements from professional/patient groups and nominated experts

There was consensus among the clinical experts and professional organisations that new agents such as tenofovir disoproxil were needed in order to combat the problem of drug resistance.

The clinical experts and professional organisations agreed that tenofovir disoproxil is an effective therapy option for people who are treatment naïve and for those with adefovir dipivoxil- and lamivudine-refractory disease. They also agreed that tenofovir disoproxil would be well tolerated by most patients.

A clinical expert said that the available RCT evidence and experience in clinical practice showed that tenofovir disoproxil was a better suppressor of hepatitis B replication than adefovir dipivoxil and lamivudine. He also said that in clinical practice, tenofovir disoproxil had shown equivalent efficacy with newer potent nucleosides such as entecavir. Another clinical expert said that

resistance appeared to emerge less frequently with tenofovir disoproxil than with other currently available antiviral agents.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer included two published cost-effectiveness studies in its submission. Both found first-line use of tenofovir disoproxil generated more quality-adjusted life-years (QALYs) and reduced medical costs compared with first-line use of lamivudine, adefovir dipivoxil or entecavir (for further details see pages 87–89 of the manufacturer's submission) .

The manufacturer submitted a Markov model that could be applied either to a cohort of people with HBeAg-positive or HBeAg-negative disease at the start of treatment. The model has 11 main states that are defined as, active chronic hepatitis B (HBV DNA ≥ 300 copies/ml), viral suppression (HBV DNA < 300 copies/ml), HBeAg seroconverted (not applicable for HBeAg-negative model), HBsAg seroconverted, compensated cirrhosis with detectable HBV DNA, compensated cirrhosis undetectable HBV DNA, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation (year in which it occurs), post liver transplantation and death. The model is designed to compare tenofovir disoproxil, adefovir dipivoxil, lamivudine and entecavir. It incorporates first-, second- and third-line treatments. Patients move on to the next treatment regimen if they develop resistance to their current treatment. For both cohorts the model has a lifetime horizon, and patients are assumed to continue to receive tenofovir disoproxil (and all other therapies) until they die, undergo HBeAg seroconversion, undergo HBsAg seroconversion or develop tenofovir disoproxil resistance.

The utilities for all states are based on published studies (for further details, see the manufacturer's submission pages 15, and 90–106). Three types of resources were identified and costed in the manufacturer's submission: drug acquisition costs, on-treatment monitoring and management costs, and health state costs – those associated with post-treatment surveillance of patients

with chronic disease as well as symptomatic management of advanced liver disease states.

The estimates of the proportion of patients in each disease state were based on data from a [redacted] hepatology clinic. Transition probabilities were based on data from the mixed treatment comparison and separate sets of transition probabilities for year 1 and year n were used for patients who are already resistant to one or more nucleos(t)ides. The manufacturer explained that because of a shortage of data on patients who are resistant to nucleos(t)ides other than lamivudine, all of the transition probabilities for resistant patients were based on those for lamivudine-resistant patients.

The base case results are summarised in tables 7 and 8 below. See also Figures 7 and 8 in the manufacturer's submission for illustration of the cost-effectiveness frontier (pages 135 and 140).

Table 7 Base-case results for the manufacturer's economic analysis; tenofovir disoproxil as first-line antiviral therapy in HBeAg-positive disease (MS table 35 page 132)

Comparison	Total QALYs/ patient	Total cost/ patient	cost/QALY vs LAM then BSC	ICER (cost/QALY) along the cost effectiveness frontier*
TDF then LAM	19.57	£28,718	£7,344	£9,940
TDF then TDF+LAM	19.60	£29,040	£7,412	£13,619

* The ICER for TDF then LAM is compared with LAM then TDF. ICER for TDF then TDF+LAM is compared with TDF then LAM.

TDF – tenofovir disproxil fumarate; LAM – lamivudine, BSC – best supportive care, QALY – quality adjusted life year, ICER – incremental cost effectiveness ratio

Table 8 Base-case results for the manufacturer's economic analysis; tenofovir disoproxil as first-line antiviral therapy in HBeAg-negative disease (MS Table 37 page 137)

Comparison	Total QALYs/ patient	Total cost/ patient	cost/QALY vs LAM then BSC	ICER (cost/QALY) along the cost effectiveness frontier*
TDF then LAM	16.41	£60,079	£9,811	£9,811
TDF then TDF+LAM	16.51	£61,455	£9,895	£13,854

* The ICER for TDF then LAM is compared with LAM then TDF. ICER for TDF then TDF+LAM is compared with TDF then LAM.

TDF – tenofovir disoproxil fumarate; LAM – lamivudine, BSC – best supportive care, QALY – quality adjusted life year, ICER – incremental cost effectiveness ratio

The ERG explained that probabilistic sensitivity analysis was not undertaken in the post-clarification version of the manufacturer's submission. However the ERG was able to undertake this analysis using data provided in the appendices of the manufacturer's submission (for details of methodology used see page 96 of the ERG report)

.The ERG analysis for HBeAg positive disease found that if the maximum acceptable amount to pay for an additional QALY gained was £20,000 then the strategies identified from the cost-effectiveness frontier in the deterministic analysis had the following probabilities of cost-effectiveness:

- Best supportive care, 6.55%
- Lamivudine then BSC, 2.05%
- Lamivudine then tenofovir disoproxil, 21.00%
- Tenofovir disoproxil then lamivudine, 35.90%
- Tenofovir then tenofovir disoproxil plus lamivudine, 20.40%
- Tenofovir then tenofovir disoproxil plus lamivudine then entecavir, 3.30%

See table 35 in the ERG report, which also gives the probabilities at maximum acceptable amounts to pay for an additional QALY of £30,000 and £50,000.

The corresponding analysis for HBeAg negative disease found that the strategies from the cost-effectiveness frontier had the following probabilities of

being cost effective if the maximum acceptable amount to pay for an additional QALY gained was £20,000:

- Best supportive care, 6.95%
- Tenofovir disoproxil then lamivudine, 17.80%
- Tenofovir disoproxil then tenofovir disoproxil plus lamivudine, 44.70%
- Tenofovir disoproxil then tenofovir disoproxil plus lamivudine then entecavir, 26.55%

See table 37 in the ERG report, which also gives the probabilities at maximum acceptable amounts to pay for an additional QALY of £30,000 and £50,000.

3.1.1 Results of the manufacturer's one-way sensitivity analyses

The manufacturer conducted sensitivity analyses for HBeAg-positive disease comparing the strategies of tenofovir disoproxil then lamivudine versus lamivudine then tenofovir disoproxil; and also of lamivudine then tenofovir disoproxil versus lamivudine then best supportive care. For HBeAg-negative disease it compared the strategy of tenofovir disoproxil then lamivudine with best supportive care.

For HBeAg-positive disease the model results were most sensitive to: the probability of HBeAg seroconversion for antiviral-naïve patients receiving tenofovir disoproxil, the probability of HBeAg seroconversion for people with lamivudine-resistant disease receiving tenofovir disoproxil, and the excess mortality associated with the viral suppression state. For HBeAg-negative disease the model results were most sensitive to: the probability of developing compensated cirrhosis from the active chronic hepatitis B state, the discount rate for costs, and the excess mortality associated with the viral suppression state.

3.1.2 Results of the manufacturer's scenario analysis

The manufacturer undertook a scenario analysis for key parameters and assumptions in the model. The time horizon was the only factor that resulted

in a cost-effectiveness estimate greater than £20,000 per QALY for both HBeAg-positive and -negative disease (for further details see manufacturer's submission page 158). At a time horizons of less than 10 years, neither first- nor second-line tenofovir disoproxil would be cost effective at a threshold of £20,000 per QALY. At time horizons between 11 and 19 years (inclusive) second-line use of tenofovir disoproxil would be cost-effective at a £20,000 per QALY threshold, but first-line tenofovir disoproxil would not.

3.2 Evidence Review Group comments

The ERG said that the structure adopted for the economic model is reasonable, and consistent with previous economic evaluations. But it had some concerns about internal (see ERG report page 75–82) and external (see ERG report page 82 section 4.3.3.2) consistency.

The ERG explained that the health state utilities were derived from published sources, and are broadly comparable with those used in the previous independent Technology Assessment Report (TAR) used in the NICE appraisal of pegylated interferon alfa-2a and adefovir dipivoxil for chronic hepatitis B (for further details see pages 69–74 of the ERG report) The ERG explained that the health state utilities used appear to be appropriate for modelling the effect of anti-viral treatment of chronic hepatitis B, although they do not strictly meet the NICE reference case, which stipulates that public (rather than patient) preferences should be used in health state valuation.

The ERG assumed that treated patients would be seen in clinic every 3 to 6 months in the model, which is less frequently than was assumed in NICE technology appraisal guidance 96 As a result, health state costs for the mild states are lower than were estimated in the previous assessment report.

Methods used to derive input data for the economic model were considered to be generally appropriate but overall the reporting of the analyses is poor, particularly in terms of searching for and critical appraisal of studies used to estimate parameter inputs. In many cases very limited information is provided on studies contributing data to key input parameters in the model.

The ERG explained that the pooled analysis of resistance (manufacturer's submission appendix 5, page 67) was used to derive the resistance probabilities in the model. There is no report any quality assessment or risk of bias with respect to included studies nor is there any discussion of the appropriateness of pooling data from studies with a variety of designs. The ERG explained that the method used to derive annual proportions was not reported but they were able to infer it from the information given. The ERG explained an alternative approach that would have the impact of reducing the estimated risk of resistance in year 3 and increasing the risk of resistance in year 4 (for further details see page 67 of the ERG report.

3.2.1 ERG's exploration of the manufacturer's model

The ERG pointed out that there were a number of analytical errors in the way that QALY outcomes were discounted in the electronic model. Discount factors for future health effects were applied to half of the model cycles (only for odd-numbered cycles, with undiscounted values for even-numbered cycles) in the manufacturer's HBeAg-positive and -negative models (for further details see pages75–82 of the ERG report) and the reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression was applied twice instead of once.

The transition matrices in the electronic model appear to have been constructed incorrectly for the chronic hepatitis B (active and viral suppression) and compensated cirrhosis (active and viral suppression) states. The effect of this error is to underestimate the probability of remaining in the current health state. (For further details see page 79 of the ERG report).However, the ERG judged that error did not appear to bias the results, primarily because an ad hoc adjustment has been made in the model to the transition matrix for tenofovir disoproxil. However, this is not an appropriate strategy to deal with an error in constructing the transition matrices and means that the matrices are inconsistent between strategies in the model.

The ERG re-ran the model with discount factors for future health effects applied to all of the model cycles, amendments to transition matrices and

applying a reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression only once.

The resulting ERG analysis for people with HBeAg-positive disease gave an incremental cost-effectiveness ratio (ICER) for first-line tenofovir disoproxil (followed by lamivudine if patients develop resistance to tenofovir disoproxil) that was approximately double that in the manufacturer's submission: £9940 reported in the manufacturer's submission, £17,590 in the ERG analysis. The ICER for tenofovir disoproxil followed by lamivudine plus tenofovir disoproxil also approximately doubled: from £13,619 reported in the manufacturer's submission to £27,479 in the ERG's amended analysis.

The ERG re-ran the analysis using its amended model (see above) and found it broadly confirmed the findings of the scenario analyses presented in the manufacturer's submission – that the cost-effectiveness estimates are largely robust to the scenarios adopted other than reducing the model time horizon, for both HBeAg-positive and -negative chronic hepatitis B.

3.3 Further considerations following premeeting briefing teleconference

- How do the comparators considered in this appraisal relate to published NICE guidance and what is the likely place of tenofovir disoproxil in the treatment pathway?
- What are the long-term concerns about the emergence of resistance?
- What are the best surrogate markers for the purposes of modelling long-term outcomes?

4 Authors

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

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

- Jones et al., Tenofovir disoproxil fumurate for the treatment of chronic hepatitis B, January 2009.

B Submissions or statements from the following organisations:

I. Manufacturer/sponsor

- Gilead Sciences (tenofovir disoproxil fumarate)

II. Professional/specialist, patient/carer and other groups:

- Association of Clinical Microbiologists
- Department of Health
- Hepatitis B Foundation UK
- Royal College of Nursing
- Royal College of Physicians