tenofovir disoproxil (as fumarate), 245 mg film-coated tablet (Viread®) No. (479/08)

Gilead Sciences

06 June 2008

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tenofovir (Viread®) is accepted for use within NHS Scotland 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.

Tenofovir has been shown to be significantly more effective than another nucleoside reverse transcriptase inhibitor in achieving a complete composite response (virological plus histological response) in a greater proportion of patients with chronic hepatitis B infection with HBeAg positive and HBeAg negative disease.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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.

This indication is based on histological, virological, biochemical and serological responses mainly in adult nucleoside naïve patients with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver function.

Dosing information

Tenofovir disoproxil (as fumarate), 245 mg once daily taken orally with food.
Treatment may be discontinued on HBsAg loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown.

Product availability date

April 2008

Summary of evidence on comparative efficacy

Tenofovir disoproxil fumarate, the oral pro-drug of tenofovir, is a nucleoside reverse transcriptase inhibitor. It inhibits viral polymerases by directly competing with the natural deoxyribonucleotide substrate and after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination.

Two similarly designed, 48-week, randomised, double-blind, active-controlled, phase lll pivotal studies, in HBeAg positive and negative patients, aged 18 to 69 years, support the indication under review. Patients remaining on treatment at 48 weeks had the option of open label tenofovir up to 240 weeks while remaining blinded to their original treatment; this part of the study is ongoing. Patients included in the studies had chronic hepatitis B viral (HBV) infection (positive serum HBsAg for at least six months, raised ALT, HBV DNA $>10^5$ copies/ml, Knodell necroinflammatory score ≥3 and Knodell fibrosis score <4). The primary endpoint was the proportion of patients with a combined virological and histological complete response at week 48, defined as suppression of HBV DNA < 400 copies/ml and at least a two-point reduction in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score. Secondary endpoints included the individual components of the primary endpoint, the proportion of patients with normal or normalised ALT and any changes from baseline at the conserved sites of HBV polymerase in patients with persistent viraemia or who experienced virologic rebound (defined as HBV DNA ≥400 copies/ml at Week 48; a confirmed value >400 copies/ml after a value <400 copies/ml; or a confirmed value 1 log above nadir after nadir occurred).

In one of the studies, 266 patients with active HBeAg positive chronic HBV infection were randomised (2:1) and treated with tenofovir disoproxil fumarate 300 mg daily (n=176) or adefovir 10 mg daily (n=90). In the other study, 375 patients with HBeAg negative and anti-HBe+ at screening, were randomised (2:1) and treated with tenofovir disoproxil fumarate 300 mg daily (n=250) or adefovir 10 g daily (n=125).

Patients in the HBeAg positive study were approximately 10 years younger than in the HBeAg negative study (34 vs. 44 years), had a higher HBV DNA viral load at baseline (8.72 log_{10} copies/ml vs. 6.90 log_{10} copies/ml and fewer had prior treatment with lamivudine/emtricitabine (3.4% vs. 18%).

Significantly more patients achieved the primary endpoint of complete response at 48 weeks in the tenofovir groups compared with the adefovir groups. The results are summarised in tables 1 and 2.

Table 1. Composite primary efficacy response outcome and primary efficacy response component outcomes at Week 48 for the study of HBeAg positive patients

Response category n (%)	Tenofovir N=176	Adefovir N=90	Difference estimate (95% CI)[†]
Complete response	117 (67%)	11 (12%)	54% (45 to 64)
Histologic response	131 (74%)	61 (68%)	6% (-5.6 to 17)
HBV DNA <400 copies/ml	140 (80%)	12 (13%)	66% (57 to 75)

[†]Difference and CI are adjusted for baseline ALT stratum. CI= confidence interval

Table 2. Composite primary efficacy response outcome and primary efficacy response component outcomes at Week 48 for the study of HBeAg negative patients

Response category n (%)	Tenofovir N=250	Adefovir N=125	Difference estimate (95% CI)[†]
Complete response	177 (71%)	61 (49%)	24% (13 to 34)
Histologic response	181 (72%)	86 (69%)	5.2% (-4.5 to 15)
HBV DNA <400 copies/ml	236 (94%)	80 (64%)	30% (22 to 39)

[†]Difference and CI are adjusted for baseline ALT stratum.

The mean reduction from baseline in HBV DNA at week 48 in both studies was significantly greater in the tenofovir groups (-6.2 log_{10} copies/ml vs. -3.9 log_{10} copies/ml in the HBeAg positive study and -4.5 log_{10} copies/ml vs. -4.1 log_{10} copies/ml for the HBeAg negative study, for tenofovir and adefovir, respectively). Other secondary outcomes favoured tenofovir in the HBeAg positive study; significantly more patients had normal or normalised ALT, five patients in the tenofovir group achieved HBsAg loss, two achieving a HBsAg seroconversion, compared to none in the adefovir group, but a similar number of patients in both groups had HBeAg loss or achieved an HBeAg seroconversion. In the HBeAg negative study there was no difference in the number of patients with normal or normalised ALT and no patients in either group had HBsAg loss or seroconverted to anti-HBs by week 48.

Summary of evidence on comparative safety

No new safety concerns were reported in the pivotal studies; in both studies the adverse event profiles of tenofovir and adefovir were similar. In the HBeAg positive study, the only notable difference was a significantly higher incidence of mild nausea in the tenofovir group (31% vs. 17%). In the HBeAg negative study there was a significantly higher incidence of arthralgia in the tenofovir group (6.0% vs. 0%).

Monitoring of renal function (creatinine clearance and serum phosphate) is recommended before initiating and during tenofovir treatment.

Summary of clinical effectiveness issues

Tenofovir has been shown to be significantly more effective than adefovir in providing a complete response in both HBeAg positive and HBeAg negative patients. However, the composite endpoint was driven by the proportion of patients with reduction in HBV DNA levels to <400 copies/ml as there was no significant difference in histological outcomes. This is the only direct comparison with another hepatitis B therapy, although indirect comparisons with entecavir, telbivudine and lamividine have been presented.

Only a small number of patients in the pivotal studies had prior experience with lamivudine or emtricitabine for more than 12 weeks (<5% in the HBeAg positive study and <20% in the HBeAg negative study) plus a number of small, non randomised studies in lamivudine resistant patients. Consequently, the evidence for tenofovir use in this patient population is limited.

All mutations known to confer drug resistance occur on conserved sites on the HBV DNA polymerase gene. In the pivotal studies, with 48 weeks of follow up, only two patients in the tenofovir group had documented mutations on the conserved site compared with 15 patients treated with adefovir. Longer-term data are required to fully establish resistance patterns to tenofovir as resistance on the introduction of adefovir was barely evident following 60 weeks of treatment. *In vitro* studies have shown that with the combination of two lamivudine resistant mutants the susceptibility of HBV to tenofovir was reduced nearly six fold.

Only lamivudine and adefovir are indicated for use in patients with both compensated and decompensated liver disease; entecavir, telbivudine and tenofovir are indicated for use in patients with compensated liver disease only.

Patients with HBsAg loss or seroconversion during the HBeAg positive study could discontinue treatment and were then followed for 24 weeks to assess durability of response. This has not yet been established so optimum duration of treatment is not known.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis. The analysis used Markov modelling to compare tenofovir to adefovir, entecavir, lamivudine, the most commonly-used combinations of these agents (adefovir plus lamivudine, entecavir plus adefovir and tenofovir plus lamivudine) and best supportive care (BSC) in a mixed cohort of patients including HBeAg positive and HBeAg negative, with or without compensated cirrhosis. Patients co-infected with HIV were excluded from the economic evaluation.

The model considered combinations of up to three active treatments and BSC to capture resistance profiles. This gave 262 possible strategies. The model had 17 disease states, one-year cycles and adopted a lifetime horizon. Where possible, clinical data came from a systematic review, augmented by data from randomised-controlled trials, observational data and expert opinion as required. The utilities, resource use and cost data came from appropriate and well referenced sources.

The base case results were that:

- lamivudine followed by BSC had an incremental cost per QALY of £8,583 relative to BSC

- tenofovir followed by lamivudine had an incremental cost per QALY of £9,096 compared to lamivudine followed by BSC.

Strategies involving lamivudine and tenofovir dominated virtually all other treatment strategies.

The results were supported by extensive sensitivity analyses.

The economic analysis was well conducted. The patient groups and pathways were complex and this was reflected in the model structure and the results. However the documentation was transparent and clear thereby facilitating critical appraisal. The results show tenofovir to be a cost-effective treatment option for its licensed indication.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

In February 2006, the National Institute of Health and Clinical Excellence published Technology Appraisal 96; Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. It recommends adefovir as an option for treatment of adults with chronic hepatitis B who have failed on or could not tolerate interferon or after treatment with lamivudine has resulted in viral resistance or in combination with lamivudine when the risk of development of lamivudine resistance is high.

In 2005, the British Association of Sexual Health and HIV published the UK National Guideline on the Management of the Viral Hepatitides A, B and C, which recommends that patients with chronic hepatitis B should be considered for therapy with lamivudine, adefovir, or interferon-alpha. These guidelines predate the availability of entecavir and tenofovir.

In 2007, the American Association for the Study of Liver Disease published their practice guidelines on chronic hepatitis. These summarised all aspects of the disease including prevention, evaluation, management and treatment options.

Additional information: previous SMC advice

In April 2005 after consideration of a full resubmission the Scottish Medicines Consortium issued the following advice; adefovir dipivoxil (Hepsera®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis B in adults with either compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. Its use is restricted to patients who demonstrate lamivudine resistance.

In October 2006, after consideration of a full submission the Scottish Medicines Consortium issued the following advice: entecavir (Baraclude®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and or fibrosis. Clinical studies have shown that entecavir is more effective than lamivudine in nucleoside naïve HBeAg positive and negative patients and in lamivudine refractory patients.

In February 2008 after consideration of a full submission the Scottish Medicines Consortium issued the following advice; telbivudine (Sebivo®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and/or fibrosis. For a number of therapeutic endpoints telbivudine proved to be equivalent or superior to a comparator nucleoside reverse transcriptase inhibitor.

Additional information: comparators

Nucleoside agents :lamivudine, adefovir dipivoxil, entecavir and telbivudine

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Tenofovir disoproxil	**245 mg daily**	**3,094**
Entecavir	0.5-1 mg daily	4,586
Adefovir dipivoxil	10 mg daily	3,822
Telbivudine	600 mg daily	3,774
Lamivudine	100 mg daily	1,015

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26/03/08. The optimum duration of treatment is unknown and varies between different patient groups.

Additional information: budget impact

The manufacturer estimated that using tenofovir first-line in 23 treatment-naïve patients per annum instead of another nucleoside agent would have a net budget impact of £4k in year 1, rising to £20k in year 5. If it is also adopted as second-line therapy for patients who develop resistance, the net budget impact of treating 28 patients per annum was estimated at £5k in year 1 rising to £25k in year 5. If tenofovir is used in 25 additional patients who do not currently receive any nucleoside therapy, there would be an additional budget impact of £76k in year 1 rising to £388k in year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 07 May 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.