Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

tenofovir disoproxil (as fumarate), 245mg, film-coated tablet (Viread®)

SMC No. (720/11)

Gilead Sciences Ltd

05 August 2011

The Scottish Medicines Consortium (SMC) 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 disoproxil (as fumarate) (Viread®) is accepted for use within NHS Scotland.

Indication under review: Treatment of chronic hepatitis B in adults with decompensated liver disease.

Interim results of an ongoing phase II study assessing the safety of tenofovir disoproxil in the treatment of chronic hepatitis B in patients with decompensated liver disease demonstrated that tenofovir was as well tolerated as another nucleoside/nucleotide analogue. Comparative efficacy was not tested in this study, but has been extrapolated from a mixed treatment comparison in treatment-naïve patients with compensated liver disease and hepatitis B e-antigen positive infection.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 September2011

Indication

The treatment of chronic hepatitis B in adults with decompensated liver disease.

Dosing Information

One tablet (245mg) to be taken once daily orally with food

Product availability date

22 July 2010

Summary of evidence on comparative efficacy

Tenofovir disoproxil (as fumarate), the oral pro-drug of tenofovir, is a nucleotide 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.

The indication under review is for an extension to the marketing authorisation. Tenofovir disoproxil (referred to as tenofovir hereafter) has previously been accepted by the Scottish Medicines Consortium (SMC) 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.

Evidence supporting the use of tenofovir in the treatment of chronic hepatitis B in adults with decompensated liver disease is from a multi-centre, randomised, double-blind, controlled phase II study primarily comparing the safety of tenofovir, emtricitabine plus tenofovir, and entecavir. Patients aged between 18 and 69 years with hepatitis B virus (HBV) DNA $\geq 10^3$ copies/mL, a previous or current Child-Turcotte-Pugh (CTP) score between seven and 12 (inclusive), an ALT <10 times the upper limit of normal, an estimated serum creatinine clearance calculated using the Cockcroft-Gault equation ≥50mL/min and with no evidence of hepato-cellular carcinoma were recruited. Patients were randomised in a 2:2:1 ratio to tenofovir 300mg (equivalent to tenofovir disoproxil 245mg) once daily, (n=45), emtricitabine 200mg plus tenofovir 300mg co-formulated as a single tablet, once daily (n=45), or entecavir (n=22) respectively. The dose of entecavir depended upon prior exposure to lamivudine (and therefore the probability of resistance mutations): patients with less than six months exposure were given a dose of 0.5mg daily and patients with evidence of lamivudine resistance or exposure ≥6 months took 1mg daily. The randomisation was stratified by CTP score (≤9 or 10 to 12) and prior lamivudine exposure. Patients not meeting pre-specified virological targets could be switched to open-label emtricitabine plus tenofovir at the investigator's discretion.

Efficacy outcomes were secondary endpoints of the study and surrogate measures were reported after 48 weeks of treatment: the proportion of patients with suppression of HBV DNA (< 400 copies/mL), change in HBV DNA from baseline, changes in prognostic scores (CTP), and loss or seroconversion of hepatitis B e antigen (HBeAg). Key results are represented in table 1.

Outcome	Tenofovir (n=45)	Emtricitabine plus tenofovir (n=45)	Entecavir (n=22)
HBV <400 copies/mL n, % (95% CI)	31/44, 70% (95% CI: 57 to 84%)	36/41, 88% (95% CI: 78 to 98%)	16/22, 73% (95% CI: 54 to 91%)
Mean change (SD) from baseline in HBV DNA* (log_{10} copies/mL)	-3.30 (1.52)	-3.72 (1.77)	-3.24 (1.92)
Mean change (SD) from baseline in CTP score	-0.8 (1.54)	-0.9 (1.50)	-1.3 (1.18)
HBeAg loss n, % (95% CI)	3/14, 21% (95% CI: 0 to 43%)	4/15, 27% (95% CI: 4.3 to 49%)	0/7, 0%
HBeAg seroconversion n, % (95% CI)	3/14, 21% (95% CI: 0 to 43%)	2/15, 13% (95% CI 0 to 30%)	0/7, 0%

Table 1: Key efficacy results at week 48.
CI = confidence interval, SD = standard deviation,
* Values below the lower limit of detection of the Taqman assay (169 copies/mL) were set to 168 copies/mL.

Similar proportions of patients in the tenofovir and entecavir groups switched to open-label treatment (11 to 14%) compared to 4.4% of patients in the blinded emtricitabine plus tenofovir group.

Summary of evidence on comparative safety

The study was designed to evaluate the comparative safety of tenofovir to the other treatments. The primary outcomes were: tolerability failure, defined as permanent discontinuation of study drug due to a treatment-emergent adverse event; and renal toxicity defined as serum phosphorous <2.0mg/dL, or an increase in serum creatinine ≥0.5mg/dL above baseline confirmed (over two consecutive visits). There was no significant difference between the groups for tolerability failure, encountered in 5.6% of patients in the tenofovir and emtricitabine plus tenofovir groups combined, compared with 9.1% of patients in the entecavir group. There was also no difference between the combined tenofovir and emtricitabine plus tenofovir groups compared with the entecavir group for renal toxicity (7.8% and 4.5% respectively).

Adverse events reported in the study were mainly thought to be features of decompensated liver disease. Adverse events related to the study treatment were reported in 18% (8/45) of patients treated with tenofovir, 16% (7/45) of patients in the emtricitabine plus tenofovir group, 9.1% (2/22) of patients treated with entecavir and 20% (2/10) in the open-label emtricitabine plus tenofovir group.

The European Medicines Agency (EMA) noted that there is no marked difference in the safety profile of tenofovir in HBV patients with decompensated liver disease compared to those with compensated disease.

Summary of clinical effectiveness issues

The study was primarily designed to assess the safety and tolerability of tenofovir in patients with decompensated liver disease. There was no significant difference in the proportion of patients who discontinued treatment due to adverse events. The study was undertaken in a small sample population, and there was no sample-size calculation reported, so the lack of difference in outcome may be due to insufficient power to detect any difference. The comparative safety data have limitations since the dose of entecavir used in the study is not the dose recently licensed (1mg daily) for the treatment of chronic hepatitis B in patients with decompensated liver disease. The study did not report the proportion of patients treated with the 1mg dose. There was no statistical comparison of efficacy endpoints in this study, so no robust conclusions on comparative efficacy can be made. The EMA acknowledged the low feasibility of performing a larger-scale study in this target population and considered the study to be "confirmatory" for efficacy in this population.

Tenofovir, and entecavir, are recommended in clinical guidelines for the treatment of decompensated patients due to their anti-viral potency and high genetic barrier to resistance profile, despite until recently being unlicensed in this population.

A published mixed treatment comparison (MTC) analysing the efficacy of anti-virals in the treatment of patients with HBeAg-positive chronic hepatitis B naïve to treatment was cited in the company's submission to support the economic case for tenofovir. However the MTC population was predominantly in patients with compensated liver disease and extrapolation to patients with decompensated liver disease is crucial to the economic case. Clinical experts consulted by SMC have advised that it is reasonable to extrapolate the efficacy to the patient group relevant to the submission.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis in the form of a Markov model estimating costs and benefits of different treatment strategies over a lifetime time horizon. The monotherapy treatment options compared were tenofovir, entecavir, lamivudine and adefovir. Adefovir-plus-lamivudine, and best supportive care (BSC) were also included as comparators. In each case BSC was the only option as a 'switch' therapy. In addition, tenofovir was considered as a 'switch' therapy after entecavir, lamivudine, adefovir, and adefovir-plus-lamivudine.

The natural history of the disease was modeled using a previously published economic model of the use of tenofovir in chronic hepatitis B, with selected parameters being updated from a literature search. The model structure allowed for differing assumptions regarding when lamivudine resistance developed. The comparative effectiveness, adverse event rate and tolerability of the treatment options came from a previously published mixed treatment comparison of the clinical evidence for the treatment options, again in chronic hepatitis B.

Utilities were drawn from a published survey of 600 people from various countries who did not have hepatitis B using the standard gamble method. Resource use and costs were taken from a previously published UK research study in the NHS HTA program.

The number of comparators included meant that multiple comparisons were possible but the feedback from Scottish clinical experts suggested that entecavir was the most realistic comparator.

In the situation where lamivudine resistance is possible from the start of the model, if entecavir is the current treatment the choices involving tenofovir are:
either to switch to tenofovir monotherapy £15,747 per quality adjusted life year (QALY) based on incremental costs of £14,435, and 0.92 extra QALYs
or use tenofovir as rescue therapy after entecavir when resistance has developed £15,622 per QALY based on incremental costs of £18,837, and 1.21 extra QALYs.

Given that both these cost per QALY figures are within the normally accepted range, the cost per QALY between these two regimes is relevant. Using tenofovir as rescue therapy after entecavir when resistance has developed costs £4,402 more then tenofovir monotherapy (£98,928 versus £94,526) and yields 0.29 more QALYs (5.79 versus 5.5) so the added cost per QALY gained is £15,227. This suggests that entecavir followed by tenofovir as rescue therapy when resistance develops is the most cost-effective choice.

Results were also presented for a situation where patients were not lamivudine-resistant but Scottish clinical experts report that resistance is common and guidelines do not support its use.

The key weakness in the economics case was that the values for many of the parameters, but most particularly the clinical effectiveness estimates, related to chronic hepatitis B and not specifically to decompensated disease. However, Scottish clinical expert opinion generally supported the assumption that the evidence from compensated disease would also apply to decompensated disease.

Despite this limitation, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Association for the Study of the Liver (EASL) published “EASL Clinical Practice Guidelines: management of chronic hepatitis B” in 2009. The guidelines recommend that patients with decompensated liver disease should be treated in specialised liver units due to the complexity of anti-viral therapy and the potential for requiring liver transplantation. To prevent recurrent reactivation, treatment is indicated even if the HBV DNA level is low. The guidelines recommend that either entecavir or tenofovir should be used due to their potency and good resistance profiles, despite the small amount of data for the safety in patients with decompensated disease. Clinical improvement may occur over three to six months, but some cases with advanced hepatic disease with a high Child-Pugh or MELD score may not benefit and require transplantation. In this situation treatment with a nucleoside/nucleotide analogue reduces the risk of HBV recurrence in the graft.

The American Association for the Study of Liver Diseases updated their practice guidelines, "Management of chronic hepatitis B" in 2009. This guideline recommends that patients with decompensated cirrhosis should be promptly initiated with a nucleoside/nucleotide analogue, aimed at delivering a rapid suppression of HBV with a low-risk of resistance. Recommended treatment regimens are; lamivudine or telbivudine in combination with adefovir or tenofovir; or entecavir or tenofovir monotherapy (although safety and efficacy in patients with decompensated cirrhosis are lacking).

Both guidelines predate the publication of the key study and licensing of tenofovir for the treatment of chronic hepatitis B in decompensated liver disease.

Additional information: comparators

The following medicines are also licensed for the treatment of chronic hepatitis B virus infection in patients with decompensated liver disease: entecavir, adefovir, and lamivudine (in combination with a second agent that does not have cross-resistance to lamivudine). Entecavir and lamivudine have not been reviewed by SMC for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Tenofovir disoproxil (as fumarate)	**245mg orally once daily with food**	**2,918**
Entecavir	1mg orally once daily on an empty stomach	4,408
Adefovir	10mg orally once daily.	3,600
Lamivudine *	100mg orally once daily	1,015*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 May 2011.

* In patients with decompensated liver disease, lamivudine should always be used in combination with a second agent without cross-resistance to lamivudine (e.g. adefovir, tenofovir). The cost per year quoted is for the lamivudine component only of any potential combination.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 7 patients in year 1 rising to 12 by year 5. Replies from experts suggest the numbers of patients are an underestimate. Based on an estimated uptake of 90% in year 1, continuing unchanged to year 5, the impact on the medicines budget was £20k in year 1 rising to £36k by year 5. The net medicines budget impact would be a saving of £7k in year 1 rising to £13k in year 5.

Savings included in the above calculation result from switching from a more expensive to a cheaper medicine and thus could be realised in cash terms.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Liaw YF, Sheen IS, Lee CM et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology (2011); 53: 62-72

Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naïve patients with chronic hepatitis B. Value Health 2010; 13(8):934-45

European Medicines Agency. CHMP variation assessment report – Type II variation EMEA/H/C/000419/II/0097 (Viread). [online] Available from http://www.ema.europa.eu [Last updated 29 October 2010]

This assessment is based on data submitted by the applicant company up to and including 14 July 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.