All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Emtricitabine/tenofovir DF (Truvada®)
Gilead Sciences Ltd

Advice No: 0507 – June 2007

Recommendation of AWMSG:

Emtricitabine/tenofovir DF (Truvada®) is recommended for use within NHS Wales as an option for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults who are treatment-naïve and in line with current BHIVA guidelines. It should only be prescribed by HIV specialists.

This report should be cited as:

All Wales Medicines Strategy Group Final Appraisal Report
emtricitabine/tenofovir DF (Truvada®) June 2007

1.0 RECOMMENDATION OF AWMSG:

The advice represents the view of the All Wales Medicines Strategy Group and was arrived at after evaluation of the evidence submitted by the manufacturers up to and including 15th January 2007. Local Health Boards and Trusts are expected to follow recommendations from AWMSG within 3 months of Ministerial endorsement. AWMSG advice is interim to NICE guidance should this be subsequently published. Individual clinicians should take account of guidance issued by NICE or AWMSG when exercising their clinical judgement, unless there is evidence to justify not doing so in the light of the particular circumstances of an individual patient.

Date: 12th June 2007

Emtricitabine/tenofovir DF (Truvada®) is recommended for use within NHS Wales as an option for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults who are treatment-naïve and in line with current BHIVA guidelines. It should only be prescribed by HIV specialists.

Key decision factors influencing the decision:
All studies included in the submission were in treatment-naïve patients; efficacy was not demonstrated for the use of Truvada® in patients who had previously received other treatments.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Truvada® (emtricitabine/tenofovir DF) is indicated in combination with other antiretroviral therapy for the treatment of HIV-1 infected adults[1].

2.2 Dosing:
The recommended dose is one tablet once daily with food. Dosage adjustment is required in renal impairment[1].

2.3 Market authorisation date: 21st February 2005[2]

2.4 UK Launch date: launched in 2005.

3.0 DECISION CONTEXT

This assessment aims to review the evidence submitted by the company on the clinical and cost effectiveness of Truvada® in the treatment of HIV-1 infected patients. Based on the current licensed indication, this assessment will consider the use of Truvada® in treatment naïve adult patients only.

Current UK guidance from the British HIV Association (BHIVA) suggests that the use of a non-nucleoside reverse transcriptase inhibitor (NNRTI), preferably an efavirenz-based highly active antiretroviral treatment (HAART), should ordinarily be the first line choice in newly diagnosed patients in whom treatment is indicated. Two nucleoside reverse transcriptase inhibitors (NRTIs) in addition to an NNRTI, preferably efavirenz, is the favoured HAART treatment regimen. Where treatment with an NNRTI is not appropriate, for example where there is primary resistance, then a boosted protease inhibitor (PI) should be considered. A co-formulated product of two NRTIs may be a

more convenient option but other issues such as relative cost, safety and baseline resistance need to be considered. Of the available co-formulations, Combivir® (zidovudine/lamivudine) is the most widely studied. Alternatives include Truvada® (emtricitabine/tenofovir DF) and Kivexa® (abacavir/lamivudine) [3,4] though longer term data on safety and resistance development are currently lacking for these products.

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company submitted four studies to present evidence regarding the clinical effectiveness of Truvada® for treatment-naïve HIV-1 patients[5-11]. Of these studies one provides a useful comparison between Truvada® and Combivir ®, which is one of its main competitors and a standard therapy option.[6,7]. The results of this study provide evidence of at least comparative efficacy between treatments for up to 96 weeks of therapy and indicate that emtricitabine and tenofovir DF individually dosed were associated with improved tolerability over co-formulated Combivir®. The additional studies provided with this submission included a Phase III open-label study that assessed the use of Truvada® as background therapy to two different regimens of boosted PI therapy (lopinavir with ritonavir, once versus twice daily) [8,9]. However this trial was not designed to specifically assess the efficacy of Truvada®. This second study was associated with a lower rate of respondents when compared (indirectly) to the first study, involving emtricitabine/tenofovir DF and Combivir®. Thus fitting with the current BHIVA guidelines which recommend that protease boosted regimens should only be considered where NNRTI-based regimens are not an option [4].

The remaining studies looked at the efficacy of emtricitabine and tenofovir DF as single agents[10,11]. It is not clear how these results can be extrapolated to the combination product.

There are no studies comparing Truvada® to the other licensed co-formulated NRTI, Kivexa®; no indirect analysis has been submitted by the company.

Currently the evidence does not support the use of Truvada® in children below the age of 18 years [1].

It is the opinion of the committee that the clinical evidence presented by the company indicates that Truvada® represents a useful treatment option for newly diagnosed adult patients who meet the criteria to receive HAART. Therapy should only be prescribed by a specialist experienced in the treatment of HIV-1 infected patients and should be in accordance with the BHIVA guidelines[4].

4.2 Review of the evidence on cost-effectiveness

The company's submission included a cost utility model that compared an emtricitabine/tenofovir DF regimen against a zidovudine/lamivudine regimen with a Markhov model describing four health states. A number of uncertainties exist in the economic model, and the risk-adjusted transition probabilities, in particular, are a probable (but untested) source of bias. The reliability of the economic evidence presented therefore comes into question, as the impact of key sources of uncertainty was not assessed. It is unknown, therefore, whether the cost-effectiveness estimates provided by the company (which appear at face value to be robust, and within what might be considered cost-effective) are valid.

The committee are of the opinion that the economic evidence presented by the company does not address the decision problem adequately, as the underlying model

of disease progression is based on dual, not triple anti-retroviral therapy. This is likely to have a significant impact on both the costs and benefits of treatment.

5.0 LIMITATIONS OF DECISION CONTEXT:

There are no comparative trials between Truvada® and Kivexa®, the other main competitor. However (indirect) analysis by the company to assess comparative efficacy, tolerability and cost between treatments would have been useful.

Using a dual anti-retroviral regimen as a comparator in the health economic analysis is not considered to be appropriate.

In the second Phase III study included in the submission it would have been preferable to assess Truvada® against a different NRTI combination with the same PI to allow a direct comparison between the efficacy of the NRTIs. Alternatively the results from this trial could have been compared, albeit indirectly, against other trials using combination NRTI therapy with a boosted PI.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company have based their submission on four studies. These include two Phase III randomised, open-label studies, [6-9] one of which is currently ongoing [6,7].Two additional studies reported in the company submission focus on the use of emtricitabine and tenofovir DF as single agents[10,11]. It would be inappropriate to extrapolate this data when the product being considered is a combination of the two and therefore may differ in clinical efficacy. This data has therefore only been considered in the context of potential safety issues that may have arisen during the course of each study.

Three of the four studies have been submitted as evidence for the therapeutic appraisal of Emtriva®.

6.1.1 Emtricitabine/tenofovir DF (plus efavirenz) versus zidovudine/lamivudine (plus efavirenz) (Study 934)[6,7]

In the first of these two Phase III trials, antiretroviral naïve adults with HIV-1 RNA levels >10,000 copies/ml, regardless of CD4 cell count, were randomised to receive a once daily regimen of 600mg of efavirenz, 200mg of emtricitabine and 300mg of tenofovir DF or 600mg of efavirenz and a fixed dose combination of 300mg of zidovudine and 150mg of lamivudine twice a day. The results of this study were assessed at 48 weeks[6] and then at 96 weeks[7] in the extension phase of the study. This study has recently been extended further and will now run for 144 weeks in total.

The primary objective was to assess the non-inferiority of the regimen emtricitabine, tenofovir DF and efavirenz to the regimen of zidovudine, lamivudine and efavirenz as measured by HIV RNA levels of less than 400 copies/ml through week 48.

The secondary objective was to assess the non-inferiority of emtricitabine, tenofovir DF and efavirenz compared with zidovudine, lamivudine and efavirenz at week 96 as assessed by HIV RNA levels of less than 50 copies/ml, less than 400 copies/ml and by changes in the CD4 cell count. No minimum CD4 cell count was required for study entry.

Results:
Five hundred and nine patients were included in the intention to treat (ITT) analysis, which excluded patients with baseline NNRTI resistance (n=8). During the trial a further 22 patients (11 in each group) were found to have HIV mutations associated with resistance to efavirenz. Excluding these patients, at week 48, 206/244 (84%) patients in the emtricitabine/tenofovir DF group and 177/243 (73%) of the zidovudine/lamivudine group reached and maintained HIV RNA levels of less than 400 copies/ml, which was the primary end point of the study (difference between two 95% confidence interval [CI]: 4 to 19%, P=0.002).

Twenty-four patients (12 from each arm) who completed the first 48 weeks of the study did not consent to continue through 96 weeks and were excluded from the results. Therefore at week 96, 463 of the original 509 patients were included in the analysis. Of these, 173 /232 (75%) patients in the emtricitabine/tenofovir DF group versus 143/231 (62%) patients in the zidovudine-lamivudine group maintained HIV RNA levels of less than 400 copies/ml, 95% CI for the difference between groups 4 to 21%, P=0.004.

At week 48, 194/244 (80%) patients in the emtricitabine/tenofovir DF group and 171/243 (70%) patients in the zidovudine/lamivudine group reached and maintained HIV RNA levels of less than 50 copies/ml (difference between two, 95% CI: 2 to 17%, P=0.02). At week 96, the difference between the groups was no longer statistically significant (67% [emtricitabine/tenofovir DF] versus 61% [zidovudine-lamivudine], 95% CI: -2 to 15% P=0.16).

At week 96, the patients treated with the emtricitabine, tenofovir DF and efavirenz regimen had a significantly greater mean increase from baseline in absolute CD4 cell counts compared to the zidovudine/lamivudine group (270 versus 237 cells/mm^3, respectively, P=0.036).

Unlike at week 48, there was a significant difference in virological rebound (defined as confirmed HIV RNA level > 400 copies/ml after achieving <400 copies/ml on one occasion) between the two groups, 2/232 (<1%) for emtricitabine/tenofovir DF and 12 (5%) for zidovudine/lamivudine, P=0.007).

Mean adherence (as measured by pill counts) did not differ over the 96 weeks between the groups (89% [emtricitabine/tenofovir DF] versus 87% [zidovudine/lamivudine], P=0.13).

Points to note:

- Though the majority of patients were randomised from the US (81%) and only 5% from the UK, it is unlikely that the results would not be applicable to a Welsh population.
- Baseline median CD4 cell counts for the two groups were within the range at which starting treatment would be considered (in accordance with BHIVA guidelines)[4]. Though no minimum or maximum CD4 cell count was included.
- All patients were treatment naïve, as per the current licensed indication[1].
- Combivir® is an appropriate comparator as it would be considered a standard treatment option for this patient group.
- The Simplification with Easier Emtricitabine and Tenofovir DF (SWEET) trial, is a 48 week Phase III open-label, randomised, parallel group study It aims to assess whether switching from co-formulated Combivir® or separate formulations of zidovudine and lamivudine to Truvada® results in resolution or prevention of zidovudine/lamivudine-treatment related adverse events. Patients

have already been recruited to this study and results are likely to be available within the next six to twelve months[5].

6.1.2 Lopinavir/ritonavir once daily (plus Truvada®) versus lopinavir/ritonavir twice daily (plus Truvada®) (Study 418)[8,9]

This second Phase III trial included in the submission is actually based on a comparative efficacy and safety trial of two regimens of a protease inhibitor, lopinavir, combined with the protease inhibitor ritonavir. Ritonavir was used in this context as a 'pharmacokinetic enhancer'.

This was a randomised open label multi-centre study of antiretroviral naïve patients. One hundred and ninety patients were randomised 3:2 to receive lopinavir/ritonavir 800/200mg once daily (n=115) or 400/100mg twice daily (n=75). All patients were assigned to tenofovir DF 300mg and emtricitabine 200mg once daily. Results were assessed at week 48[8] and 96; the results presented here are from week 96[9].

The proportion of patients who had a HIV RNA below 50 copies/ml was assessed using an intent-to-treat non-completer failure (ITT NC=F) method, in which missing values were considered failure unless the immediately preceding and following values were below 50 copies/ml.

Results:
A similar proportion of patients achieved HIV RNA below 50 copies/ml in both groups (57% versus 53%, once daily versus twice daily, respectively). Based on the ITT NC=F analysis, the 95% CI for the difference in response rates between the two groups was -10 to 19%, indicating non-inferiority of the lopinavir/ritonavir once daily regimen compared to the twice daily regimen. Similarly the FDA defined time to loss of virological response[14] was similar between groups, at week 96 the response rates were 57% and 55% for the once daily versus the twice daily regimen, respectively. CD4 cell count mean increases from baseline were comparable between treatment groups.

Points to note:

- This study was not designed to specifically assess the clinical efficacy of emtricitabine and tenofovir DF in combination but to compare different regimens of boosted PI. As such it provides limited evidence in support of this submission.
- If this study is compared indirectly to study 934 (7.1.1), the number of respondents who achieved HIV RNA levels below 50 copies/ml was lower.
- Current guidelines from BHIVA recommend that a (boosted) PI in combination with two NRTIs should be reserved for when an NNRTI (with two NRTIs) is unsuitable[3,4].

6.2 Safety:

The assessment of safety in Study 934 (Section 6.1.1) at week 96, comprised of 511 patients who had received any study medications[7]. Grade II to IV adverse events, in accordance with the modified Common Toxicity Criteria, were comparable between groups (182/257 (72%) [emtricitabine/tenofovir DF] versus 180/254 (71%) [zidovudine/lamivudine]).Significantly more patients in the zidovudine/lamivudine group (11%) experienced adverse events resulting in discontinuation compared to the emtricitabine/tenofovir DF group (5%), P=0.008. Most discontinuations in the zidovudine/lamivudine group occurred within the first 48 weeks of treatment and were due to anaemia[6]. No patient discontinued treatment because of anaemia from weeks 48 through 96[7].

Patients who received emtricitabine/tenofovir DF had a lower mean increase in fasting total cholesterol than those receiving zidovudine/lamivudine (25mg/dl versus 38mg/dl, P<0.001), which converts to an absolute difference between groups of 0.34mmol/L. There was no significant difference in increase in mean fasting triglycerides or low density lipoprotein (LDL). Though there was a significant increase in high density lipoprotein (HDL) in the zidovudine /lamivudine group (13mg/dl) compared with the emtricitabine/ tenofovir DF group (10mg/dl), P=0.022. No confidence intervals were supplied with these P values.

Lipodystrophy has been associated with zidovudine. Among the patients who had dual energy x-ray absorptiometry (DEXA) scans at weeks 48 and 96, a significant median loss in limb fat was observed in the zidovudine group (n=44) -0.7kg, P=0.001, whereas in the tenofovir DF group (n=49) there was a significant median gain in limb fat (0.3kg, P=0.01) [5]. Due to the increasing concern over long-term complications of lipoatrophy with zidovudine, BHIVA guidelines recommend that all patients receiving zidovudine have DEXA scans during treatment[3].

Through 96 weeks patients receiving emtricitabine/tenofovir DF in Study 934 had a significantly greater median increase from baseline in weight of 2.7kg compared with 0.5kg in patients receiving zidovudine (P<0.001). No confidence interval was supplied with this P value.

In the boosted protease study (Study 418) discontinuations from the trial were mainly due to adverse events, diarrhoea being the most common adverse event[8,9]. This is a common side effect associated with protease inhibitors but may also be associated with the use of Truvada® [1].

Concern has been raised over the potential adverse effects of tenofovir DF on renal function. Baseline testing and routine monitoring of urea, electrolytes and urinalysis are required for patients receiving tenofovir DF[3]. Truvada® should not be given to patients who have severe renal impairment[1,5].

In study 418 over 98% of patients had a serum creatinine within the therapeutic range for an adult male [8,9]. One subject in each group, both of whom received tenofovir, developed acute renal failure (defined as a serum creatinine over 3mg/dl). Renal function improved in both patients following discontinuation of the study drug, with serum creatinine levels returning to below 1.7mg/dl[8,9].

Despite these reports, no discontinuations due to renal toxicity have been reported following 192 weeks of tenofovir DF, lamivudine and efavirenz[11,12].

Decreases in bone mineral density of the spine and changes in bone biomarkers have been reported in a trial of tenofovir DF versus stavudine at 144 weeks. This occurred to a greater extent in those patients receiving tenofovir DF. A decrease in hip bone mineral density was noted at week 96. Fractures, mainly due to trauma, were reported in 11 patients in the stavudine group and five patients in the tenofovir DF group at 144 weeks[1,11]. This potential risk should be considered when prescribing Truvada® long term®.

Hyperpigmentation was reported more commonly in the emtricitabine/tenofovir DF group (n=7) versus the zidovudine/lamivudine group (n=4) in the first 48 weeks of Study 934[6].

In the company submission no comparison has been undertaken between Truvada® and Kivexa® but the following information is included here for completeness. Kivexa® can cause hypersensitivity reactions in approximately 5.4% of those patients receiving treatment[13]; most commonly in the first six weeks of therapy[1,3]. Monitoring for reactions is currently recommended. A genetic test is available to screen for the HLAB*5701 allele, carriers of whom are more likely to develop a hypersensitivity reaction, however this test is not routinely recommended at present[3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

The main competitors are the two combination NRTIs lamivudine/zidovudine (Combivir®) and abacavir/lamivudine (Kivexa®).

7.2 Comparative effectiveness:

The main comparative study (zidovudine/lamivudine versus emtricitabine/tenofovir DF) is included in the clinical effectiveness section of this report (refer to section 6.1). Comparative safety issues have been discussed under section 6.2.

Kivexa® has been shown to have similar activity to Combivir® but with reported higher CD4 cell counts than Combivir® achieved at 48 weeks[14].

Adherence:

In their submission the company discuss the issue of adherence/compliance to medication; stating that higher rates of patient adherence have been shown to correlate with successful virological outcome and increase in CD4 cell counts. As Truvada® is available as a once daily regimen this has perceived benefits regarding adherence over Combivir® which is a twice daily regimen. In study 934 no significant difference in adherence, as measured by pill counts, was observed between those patients receiving emtricitabine/tenofovir DF and those receiving zidovudine/lamivudine. Obviously this is based on data from a clinical trial setting and may not reflect everyday living; in addition patients received tenofovir DF and emtricitabine as separate tablets rather than as a co-formulated tablet. Of note, Kivexa®, an alternative NRTI combination product is also a once daily formulation[15].

Quality of life:

There are no data included in the submitted trials assessing quality of life. This is likely to be complicated by the open-label nature of the studies included in the submission. The company have attempted to address this by considering previous work that derived health state utilities for patients with HIV, stratified according to CD4 counts; indicating the higher the CD4 cell count the greater the utility score. The company have simply stated that treatment with emtricitabine and tenofovir DF maintains high CD4 counts and therefore improves long-term quality of life. However this does not appear to take into account treatment-related adverse events that may affect quality of life.

Resistance:

The BHIVA guidelines recommend resistance testing in all newly diagnosed patients who are eligible for treatment. Pre-treatment drug resistance influences the choice of NRTI backbone, although it is acknowledged in the guidelines that presently 'there is no discernible increase in the rate of NRTI mutations in recently infected patients'[3,4].

In study 934, genotypic data were collected at week 48 on 35 patients who met the criteria for resistance analyses[6]. Overall there were no significant differences between groups. At week 96 there was a significant difference between the two groups in terms of M184V mutation two in the emtricitabine/tenofovir DF group and nine in the zidovudine/lamivudine group, P=0.036 [7]. There were no significant differences in the frequency of efavirenz resistance in the two groups.

In study 418, genotypic testing was available for 23 patients who experienced a rise in HIV RNA to above 500 copies/ml occurring at any time from week 12 to 96. Overall four patients demonstrated resistance to emtricitabine (M184V/I mutations in reverse transcriptase) and none to tenofovir DF[9].

The company suggest that for patients who do not have baseline M184V mutation (responsible for resistance to lamivudine, emtricitabine and zalcitabine) emtricitabine and tenofovir DF are likely to be highly effective as second-line or switch therapy[5]. However, in line with the licensed indication, Truvada® has not been studied in patients who have received prior antiretroviral therapy and therefore cannot be recommended in this population at this time.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issue for AWMSG to consider

The key economic issues for the AWMSG to consider are:

1. whether the additional benefits offered by Truvada® over relevant comparators justify the additional costs, and if so,
2. whether the total budgetary impact of supporting the use of Truvada® is acceptable

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted have not identified any other published economic studies of the use of Truvada®.

8.3 Review of company submission on cost-effectiveness

NB: the same evidence on cost-effectiveness was provided for emtricitabine (Emtriva®) and the emtricitabine/tenofovir DF combination product (Truvada®).

8.3.1 Summary of the evidence:

The company submission included a cost-utility model that compared an emtricitabine/tenofovir DF regimen against a zidovudine /lamivudine regimen. A Markov model was constructed that described four health states: (i) CD4 cell count >200 and <500 cells/mm^3, (ii) CD4 < 200 cells/mm^3, non AIDS (iii) AIDS, and (iv) death.

For the zidovudine /lamivudine regimen, the transition probabilities used in the Markov model have been derived from two patient cohorts that were treated with dual nucleoside analogue therapy at the Royal Free Hospital, London, in 1995–6. Dual nucleoside analogue therapy is not considered an appropriate comparator, as patients did not receive a NNRTI such as efavirenz or a boosted PI in addition to their dual nucleoside analogue therapy. Treatment options were more limited in 1995-6, and this will have a major impact on the relevance of the model to today's therapy.

For the emtricitabine/tenofovir DF regimen, transition probabilities have been derived by adjusting the transition probabilities for zidovudine /lamivudine dual therapy using the relative risk of treatment failure (at week 48 in study 934) with emtricitabine/tenofovir DF *plus efavirenz* compared with zidovudine /lamivudine *plus efavirenz*. Therefore, the model uses triple therapy-derived transition probabilities for the emtricitabine/tenofovir DF regimen and dual therapy-derived transition probabilities for the zidovudine /lamivudine regimen, despite the fact that the zidovudine /lamivudine regimen in study 934 also included efavirenz. This relative risk of treatment failure was applied to all transition probabilities in the Markov matrix, including for instance, the risk of death from AIDS.

The base-case model assumes that the treatment benefit with the emtricitabine/tenofovir DF regimen (the reduced risk of treatment failure compared with the zidovudine /lamivudine regimen at 48 weeks) persists for two years, after which the transition probabilities revert to those of zidovudine /lamivudine. However, efficacy data up to 92 weeks (almost two years) is available from study 934, which indicates that a treatment benefit remains, but is lower than that observed at 48 weeks.

The assumptions made to derive the transition probabilities for the Markov matrix are not valid, and could potentially bias the model in favour of the emtricitabine/tenofovir DF regimen. The company submission fails to discuss these points.

The model considers only direct costs from the perspective of the NHS Wales. Adverse events associated with emtricitabine/tenofovir DF or zidovudine /lamivudine treatments

have not been incorporated and no consideration is given to any personal and social service costs/resource use. These could feasibly be substantial for this patient group. The model was not included with the company's submission, so analyses could not be verified. It should be noted that the cost of zidovudine is likely to decrease when generic substitutes become available.

The utility values used in the model were derived from a Canadian cohort. As these were obtained pre-2000, it is uncertain how representative they are for Welsh patients today. The blanket application of these utility values to the hypothetical cohorts run through the Markov model does not take account of the potentially different adverse event profiles and quality of life experienced by patients receiving the emtricitabine/tenofovir DF regimen versus the zidovudine /lamivudine regimen. Furthermore, the economic model assigned a fixed proportion of patients being symptomatic or asymptomatic in each of the defined health states. It is unclear how valid this assumption is, or the impact it may have on the results.

Healthcare resource use data associated with inpatient, outpatient and day ward services were derived from a national resource data collected from clinics across the UK in 2002. Community care services data were derived from a prospective cohort study conducted in London between 1992 and 1993. These data were transformed to match the health states defined by the Markov model using assumptions based on data that is over 12 years old. It is feasible that the patterns of healthcare resource use today would be significantly different from those in 1992–3, or even in 2002. There is, therefore, a degree of uncertainty with the assumed healthcare resource use data used in the model.
The costs associated with these healthcare resources have been inflated to 2006 prices.

8.3.2 Summary of key findings from the company submission in cost-effectiveness:

In the base case analysis, the incremental cost per life year gained with the emtricitabine/tenofovir DF regimen compared with the zidovudine /lamivudine regimen was £14,806. The incremental cost per QALY was £18,229. This was based on emtricitabine/tenofovir DF providing an additional 0.61 years of life and an additional 0.5 QALYs at an additional cost of around £9,000.

Several one-way sensitivity and threshold analyses were conducted, which indicated that the relative risk of disease progression (obtained from study 934), the timing of the start of treatment (initial health state) and the discount rate were the most influential parameters (of those tested). Probabilistic sensitivity analysis was conducted to assess the joint effects of uncertainty across key parameters. From this, the mean incremental cost per QALY was estimated at £18,900 (95%CI £12,000–£32,300).

However, the impact of the assumptions that are likely to be most influential on the results – those relating to the Markov transition matrix – were not assessed.

8.4 Review of evidence on budget impact

8.4.1 Summary of the evidence and key findings:

The perspective adopted by the budget impact analysis is that of NHS Wales. Welsh prevalence data from 2004 (676 cases) and incidence data for 2005 (118 incident cases) have been used to estimate the total number of people with HIV in Wales in 2005 (794). Using an assumed increase in patient numbers of 10% per year, it is estimated that between 2006 and 2010 the total number of patients with HIV/AIDS in Wales will rise from 873 to 1,278. This assumes there will be no deaths from HIV-

related illness. No justification is provided for this assumed 10% increase in patient numbers (and the 2005 incidence figures quoted actually represent 17% of the prevalent cases in 2004).

Based on 2004 data, the company submission estimates that 678 HIV infected patients (around 78%) would have been eligible for treatment with emtricitabine in 2006. Assuming a 10% increase in eligible patient numbers per year (as above), the budget impact analysis estimates that by 2010 the number of patients eligible for emtricitabine treatment will be 993 per year.

Based on BNF list prices (2006),[15] Truvada® will cost £5,022 per patient per year. This is equal to the cost of the two single agents. The budget impact analysis assumes that, in 2006, 114 of the 678 patients eligible for treatment in Wales received the Truvada® at a cost of £572,508, but from 2007 onwards prescribing of Truvada® will be more limited. The company expects that a triple combination product (emtricitabine/tenofovir DF/ efavirenz) will become available in 2007 and, based on market share estimates and commercial data (company data on file), will account for 24% of the total number of patients receiving emtricitabine/tenofovir DF. Therefore, in 2007, 107 patients are expected to receive Truvada® at an acquisition cost to NHS Wales of £537,354. In 2008–10, the triple combination product is expected to account for 70% of the emtricitabine/tenofovir DF prescribing, so Truvada® is expected to be used to treat 51 patients in 2008 at a cost of £537,354, 62 patients in 2009 at a cost of £311,364, and 75 patients in 2010 at a cost of £376,650. The budget impact analysis has not identified any direct savings with the use of Truvada® or influences on the uptake of other therapies.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- The British HIV Association produces guidelines on the management of adult patients with HIV and AIDS. These guidelines recommend that an NNRTI-based HAART regimen is used for newly diagnosed patients with HIV infection for whom treatment is indicated; usually given in combination with two NRTIs. Truvada® would therefore be considered as a first line treatment option for this patient group. Treatment choice should be tailored to the individual patient and would be dependent upon factors such as adverse effects, baseline resistance, hypersensitivities and co-morbidities.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV related treatment or care[16].
- Truvada® is currently not deemed suitable for shared care.

9.2 Previous AWMSG advice

Enfurvitide (Fuzeon®) –accepted for use (supported with restrictions, May 2004) [17].

9.3 New formulation

A once daily combination tablet of Truvada® (emtricitabine/tenofovir DF) and Sustiva® (efavirenz) is being submitted to the EMEA for market authorisation. A therapeutic drug assessment (TDA) submission by the company is recommended for appraisal by AWMSG, pending market authorisation[2].

9.4 Medical Expert

Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Group

A patient interest group submission by the Terrence Higgins Trust was provided to AWMSG members.

Glossary

Lipodystrophy: a disturbance of fat metabolism that involves the absence of fat and/or the abnormal distribution of fat in the body. Currently, "lipodystrophy" is not clearly defined and the term is used to refer to a variety of syndromes, including wasting in the face and extremities, an accumulation of abdominal fat and breast enlargement. The cause is unknown, but it could be a result of HIV infection and/or antiretroviral therapy[18].

References

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APPENDIX 1

Additional Clinical Information

The British HIV Association (BHIVA 2005)[4] recommends commencing treatment when the:

- patient becomes symptomatic (with the possible exception of those infected with pulmonary tuberculosis)
- CD4 count falls below 200 cells/mm^3
- CD4 count falls to between 201-350 cells mm^3, treatment is then dependent upon patient preference and individual risk factors.

Treatment should be deferred if the CD4 count is above 350 cells mm^3.

The objective of initial therapy is to suppress the virological response (HIV RNA concentrations) to below 50 copies/ml. Therapy should be switched if this is not reached or where it has been previously reached but now there is persistent viral rebound defined as: greater than 400 copies/ml on two occasions at least one month apart having previously been undetectable, or never reaching undetectable. An assessment of the factors affecting plasma levels should be undertaken, for example poor adherence, drug interactions, intolerability or resistance.

The Working group of the Office of AIDS Research Advisory Council (OARAC)[19] in the US recommend that each patient initially entering care should have a complete medical history, full examination and laboratory tests (HIV antibody test, CD4 T cell count, plasma HIV RNA, full blood count, fasting blood glucose, lipid profile and resistance testing before patients commence therapy). To also determine the presence of co-infections, assess overall health, economic and social issues.

The CD4 cell count serves as the most important indicator of immune status and when to start treatment. It is a strong predictor of disease progression and survival. Accordingly the CD4 cell count should be monitored every 3-6 months. Adequate viral suppression is defined as an increase of 100-150cells/mm3 per year with an accelerated response in the first three months, then 100 cells/mm3 until a threshold is reached. Viral load may be used to assess the need to start treatment but also to assess continued response as a surrogate marker. One key goal is to attain a viral load of <50 copies/ml by 16-24 weeks. Other treatment goals are to reduce HIV morbidity and mortality, improve quality of life, restore and improve immunological function and maximally and durably suppress viral load. Virological failure can be defined as a confirmed HIV RNA level > 400 copies/ml after 24 weeks, >50 copies after 48 weeks or a repeated HIV RNA level >400 copies/ml after prior suppression to < 400 copies/ml.

The Working group state that most experience is associated with the use of one NNRT and two NRTIs or one PI (with or without ritonavir boosting) and two NRTIs.

APPENDIX 2

Health economic review

Review of published evidence on cost-effectiveness

Standard searches conducted across multiple databases and information portals have not identified any other published economic studies of the use of emtricitabine/tenofovir DF.

Company submission - economic evidence

1. Description of company submission

The company submission included a cost-utility model that compared an emtricitabine/tenofovir DF regimen against a zidovudine/ lamivudine regimen[5]. A Markov model based on that constructed by Chancellor et al 1997[20] was employed. It is unclear why this model was chosen in preference to others, and no analyses were undertaken with alternative models.

Disease progression was modelled using four distinct health states: (i) CD4 cell count >200 and <500 cells/mm^3, (ii) CD4 < 200 cells/mm^3, non AIDS (iii) AIDS, and (iv) death. This model structure is likely to adequately represent the disease state and progression, but a limitation is the assumption that disease progression cannot be reversed (as is possible with HAART). In line with previous models, a 1-year cycle length was chosen, as clinical trials typically have analysed data at 48 weeks. Appropriate half cycle corrections appear to have been made. The model was not included with the company submission so analyses could not be verified. There are major issues around the transition probabilities used in the model, which may have the effect of biasing the analyses in favour of emtricitabine regimens (see sections 4 and 5.1).

2. Population

The model was simulated with a hypothetical cohort of 1000 patients who were representative of participants in study 934. This is an ongoing, phase III, open-label trial that enrolled 517 antiretroviral treatment-naïve HIV-infected adult patients who had baseline HIV-1 RNA levels >10,000 copies/ml. Mean CD4 cell count in the emtricitabine and control groups were 245cells/mm^3 and 241cells/mm^3, respectively (see section 6.1 of main document)[6,7]. The majority of patients were US-based (81%) and 5% were UK-based. This patient population is likely to adequately represent the adult HIV patient population in Wales. Though emtricitabine is licensed for use in children[21], Truvada® is not[1], in addition neither study 934 nor the cost-effectiveness analysis are applicable to children under 18 years of age.

3. Perspective and time horizon

The model considers only direct costs from the perspective of the NHS Wales. No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for this patient group.

The time horizon chose for the analysis was 20 years. A sensitivity analysis was conducted to assess the impact of varying this time horizon.

4. Comparator

The economic model compares emtricitabine/tenofovir DF with the current standard nucleoside backbone of zidovudine /lamivudine. This is an appropriate dual nucleoside

analogue comparator as indicated by recent British HIV guidelines[3]. However, the guidelines also state that treatment should also include either an NNRTI or a boosted PI. Study 934 participants who received emtricitabine/tenofovir DF or zidovudine /lamivudine also received efavirenz, which is in line with these guidelines. However, in the model it would seem that the effects of efavirenz have been neglected for the patients receiving the zidovudine/lamivudine regimen (see section 5.1).

There are other HAART regimens that would also be suitable comparators and this analysis does not provide information in relation to any of these.

5. Clinical inputs

5.1. Efficacy

Baseline status

The baseline CD4 cell counts of the hypothetical cohort, which define the proportion of patients in each of the four distinct health states at the start of the first cycle of the model, were assumed to be the same as the baseline CD4 cell counts observed in patients enrolled into study 934.

Transition probabilities

For the zidovudine /lamivudine regimen, the transition probabilities used in the Markov model appear to have been obtained from a paper by Trueman et al 2000[22]. This study used data from two patient cohorts that were treated with dual nucleoside analogue therapy at the Royal Free Hospital, London in 1995 and 1996. There are a number of uncertainties with the use of these data, which are not discussed in the company submission. These include, for instance, the fact that treatment options were more limited in 1995-6, which may have resulted in patients not being very adherent with their treatment regimens due to adverse effects, resulting in poorer outcomes than would be achieved today; and that no information on co-morbidities that might have contributed to disease progression is considered. These historical control patients did not receive an NNRTI (such as efavirenz) or a boosted PI in addition to their dual nucleoside analogue therapy.

For the emtricitabine/tenofovir DF regimen, the transition probabilities used in the Markov model have been derived by adjusting the transition probabilities for zidovudine /lamivudine dual therapy (taken from Trueman et al 2000)[22] using the relative risk of treatment failure (defined as a HIV-1 RNA viral load >400copies/ml at week 48) with emtricitabine/tenofovir DF *plus efavirenz* compared with zidovudine /lamivudine *plus efavirenz* as observed in study 934. To use the triple therapy-derived transition probabilities for the emtricitabine/tenofovir DF regimen and the dual therapy-derived transition probabilities for the zidovudine /lamivudine regimen in the Markov model could potentially bias the model in favour of the emtricitabine/tenofovir DF regimen. The company submission fails to discuss this.

This relative risk of treatment failure was calculated as 0.539 (95% CI, 0.416 to 0.844) and applied to all transition probabilities in the Markov matrix. This, in effect, assumes that the risk progression to AIDS from the [200< CD4 <500] health state is also reduced by a factor of 0.539. Likewise the risk of death from AIDS is also reduced by the same amount. This is a major assumption that is not supported by available evidence.

The base-case model assumes that the treatment benefit with the emtricitabine/tenofovir DF regimen (the reduced risk of treatment failure compared with the zidovudine /lamivudine regimen) persists for two years, after which the transition probabilities revert to those of zidovudine /lamivudine. This was based on the same assumption used in previous cost-effectiveness studies of other agents, including those

by Chancellor et al 1997 and Trueman et al 2000[20,22]. However, these previous studies had to make an assumption on the duration of treatment effect, as actual efficacy data beyond one or two years for the agents considered were not available. In contrast, study 934 has efficacy data up to 92 weeks (almost two years) and is now planned to continue up to 144 weeks. The relative risk of treatment failure at 92 weeks is 0.658, indicating that the transition probabilities are time-dependent, not time-invariant as specified in the company's submission.

5.2. Health Outcomes

Utility values used to weight the life years gained estimated by the model were the same as those used in the Trueman et al study 2000[22]. These were derived from a Canadian cohort using the Health Utility Index. Utility weights were obtained for those with CD4 counts between 200 and 500cells/mm^3, less than 200cells/mm^3, and those with AIDS. As these data were obtained pre-2000, it is possible that the quality of life of patients in these states would have been worse than would be experienced today, due to the burden of adverse events with medication in the context of fewer treatment options. Although HAART treatment regimens would have been available from 1997 onwards, it is not certain what proportion of patients were receiving triple therapy or what that therapy was. The blanket application of these utility values to the hypothetical cohorts run through the Markov model does not take account of the potentially different adverse event profiles and quality of life experienced by patients receiving the emtricitabine/tenofovir DF regimen versus the zidovudine /lamivudine regimen. This, therefore, introduces uncertainty into the cost-utility analysis. Although utility values were one of the parameters tested in the probabilistic sensitivity analysis, utilities from alternative sources were not tested in the model.

5.3. Adverse events

Adverse events associated with emtricitabine/tenofovir DF or zidovudine /lamivudine treatments have not been incorporated into the model.

6. Healthcare resource utilisation and cost

The model considers only direct healthcare resources and costs. No consideration is given to any personal and social service resources or costs, which is a limitation of the model as these could feasibly be substantial for this patient group. Resource use and costs of adverse events with treatment have not been incorporated in the model explicitly.

Healthcare resource use data associated with inpatient, outpatient and day ward services were derived from a national monitoring programme for HIV, which included resource data from over 21,000 HIV-infected patients treated in 12 clinics across the UK in 2002. This programme collected data on patients that were stratified into three groups: asymptomatic HIV infection, symptomatic non-AIDS, and AIDS.

Community care services data were derived from a prospective cohort study conducted in 235 HIV-infected individuals over a six month period in London between 1992 and 1993[23]. This study also stratified patients into the same three groups.

As HIV/AIDS status in study 934 was defined by CD4 cell counts, rather than on the basis of patients being asymptomatic or symptomatic, it was necessary to transform the resource data. This was done using assumptions adopted in the Chancellor et al 1997 study, which are actually based on data collected from 1987 to 1995. These assume that 86% of patients with a CD4 count between 200 and 500cells/mm^3 and 46% of non-AIDS patients with a CD4 count less than 200cells/mm^3 would be asymptomatic. The reliability of these assumptions, based on data that is over 12 years old, is unclear, and not tested by sensitivity analysis.

It is feasible that the patterns of healthcare resource use today would be significantly different from those in 1992–3 or even in 2002. There is, therefore, a degree of uncertainty with the assumed healthcare resource use data used in the model.

The costs associated with these healthcare resources have been estimated by applying 1996 unit costs derived from a UK study for inpatient, outpatient and day ward visits, and inflating these to 2006 prices. The costs for community care appear to have been inflated from the 1992–3 community care services data. The reliability of inflating costs over such a long time horizon is questionable.

Daily drug costs have been taken from the BNF[15]. It is worth noting that zidovudine and lamivudine used in the trial and model are presented as a combination product (Combivir®). The impact of the price of zidovudine /lamivudine on the model has been tested by sensitivity analysis.

7. Discounting

In the base case analysis, costs and outcomes were discounted at 3.5% after year 1. Sensitivity analysis on the discount rate was conducted.

8. Results

8.1. Base-case analysis of the cost-effectiveness model

Over a time horizon of 20 years, using a discount rate of 3.5% and assuming that treatment benefit with emtricitabine/tenofovir DF persisted for two years, the incremental cost per life year gained with the emtricitabine/tenofovir DF regimen compared with the zidovudine /lamivudine regimen was £14,806. The incremental cost per QALY was £18,229. This was based on emtricitabine/tenofovir DF providing an additional 0.61 years of life and an additional 0.5 QALYs at an additional cost of around £9,000.

8.2. Sub-group analysis

No subgroup analysis has been presented in the company submission.

9. Sensitivity analysis

Sensitivity analyses were restricted to parameter uncertainty and discount rate. Several one-way sensitivity and threshold analyses were conducted (9.1–9.6), which indicate that the relative risk of disease progression (obtained from study 934), the timing of the start of treatment, and the discount rate are the most influential parameters; however, the model is relatively stable to changes in these parameters. A probabilistic sensitivity analysis is also presented in the company submission (9.7).

Importantly, no attempt was made at assessing the impact on cost-effectiveness of the transition probabilities, or the proportion of symptomatic / asymptomatic patients, categorised by CD4 cell count.

9.1 Relative risk of disease progression

The relative risk of treatment failure at 48 weeks in study 934, which was used to derive the transition probabilities for emtricitabine/tenofovir DF, was 0.593 (95% CI, 0.416 to 0.844). Using the lower and upper bounds of this confidence interval, the incremental cost per QALY ranged from £16,476 to £26,731.

9.2 Duration of treatment benefit

Varying the duration of treatment benefit (based on the relative risk of treatment failure at 48 weeks in study 934) from 1 year to 8 years produced incremental costs per QALY of £18,728 to £19,112.

9.3 Timing of the start of treatment

At the start of treatment, patients in the hypothetical cohort can be in one of three health states: (i) CD4 count between 200 and 500cells/mm^3, (ii) CD4 count < 200cells/mm^3 but not with AIDS, or (iii) AIDS. The incremental cost per QALY if all patients started treatment in health state (i), (ii), or (iii) were £16,046, £17,948, or £25,018, respectively.

9.4 Cost of drug treatment

Threshold analysis indicated that, at a constant cost for emtricitabine/tenofovir DF, the incremental cost per QALY would exceed £20,000 if the daily cost of zidovudine /lamivudine was reduced by 15%. A £30,000 per QALY threshold would be exceeded if the cost of zidovudine /lamivudine reduced to £1 per day.

9.5 Time horizon

Adopting a time horizon of 10 years, instead of 20 years as in the base case analysis, the incremental cost per QALY increased very slightly to £18,650. At 5 years this increased to £20,443, suggesting that the model is relatively insensitive to the time horizon adopted.

9.6 Annual discount rate

Varying the discount rate applied to the benefits and costs between 0% and 6% yielded a worst case incremental cost per QALY of £23,835 (costs discounted at 1.5%; benefits at 6%) and best case incremental cost per QALY of £14,004 (costs discounted at 6%; benefits at 1.5%).

9.7 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted by assigning distributions to parameters of the base-case model. A lognormal distribution was assigned to the relative risk statistic, and beta distributions assigned to health state utilities, which seem appropriate. The time horizon for the analysis (20 years), the discount rate (3.5%) and the daily drug acquisition costs were fixed. For the costs of healthcare resource use (which were estimated by applying unit costs to counts of resource use), the company submission states that a normal distribution was assigned. However, costs are not normally distributed: a lognormal distribution or gamma distribution may have been more appropriate, and the impact of this on the subsequent analysis is unclear.

A Monte Carlo simulation of 10,000 patients was run on the model and a cost effectiveness acceptability curve was generated. The mean incremental cost per QALY was estimated at £18,900 (95% CI, £12,000 to £32,300). The probability of emtricitabine/tenofovir DF being cost-effective at a willingness to pay threshold of £30,000 per QALY was >95%.

Company submission - budget impact analysis

The perspective adopted by the budget impact analysis is that of NHS Wales. Welsh prevalence data from 2004 (676 cases) and incidence data for 2005 (118 incident cases) obtained from Health Protection Agency Centre for Infections have been used to estimate the total number of people with HIV in Wales in 2005 (794)[24,25]. Using an assumed increase in patient numbers of 10% per year, it is estimated that between 2006 and 2010 the total number of patients with HIV/AIDS in Wales will rise from 873 to 1,278. This assumes there will be no deaths from HIV-related illness. No justification is provided for this assumed 10% increase in patient numbers (and the 2005 incidence figures quoted actually represent 17% of the prevalent cases in 2004).

Based on Welsh data obtained from Health Protection Agency Centre for Infections, the company submission states that, in 2004, 525 individuals with HIV were either already receiving HAART or had CD4 counts <350cells/mm^3. It is not clear how this figure has been derived from the reference stated, but using this proportion of 2004 cases (almost 78%), the company submission estimates that 678 HIV infected patients would have been eligible for treatment with emtricitabine in 2006. Assuming a 10% increase in eligible patient numbers per year (as above), the budget impact analysis estimates that by 2010 the number of patients eligible for emtricitabine treatment will be 993 per year.

Based on BNF list prices (2006)[15], Truvada® will cost £5,022 per patient per year. This is equal to the cost of the two single agents. The budget impact analysis assumes that, in 2006, 114 (17%) of the 678 patients eligible for treatment in Wales received the emtricitabine/tenofovir DF combination product (Truvada®) at a cost of £572,508, but from 2007 onwards prescribing of Truvada® will be more limited. The company expects that a triple combination product (emtricitabine/tenofovir DF/efavirenz) will become available in 2007 and, based on market share estimates and commercial data (company data on file), will account for 24% of the total number of patients receiving emtricitabine/tenofovir DF. Therefore, in 2007, 107 patients are expected to receive Truvada® at an acquisition cost to NHS Wales of £537,354. In 2008–10, the triple combination product is expected to account for 70% of the emtricitabine/tenofovir DF prescribing, so Truvada® is expected to be used to treat 51 patients in 2008 at a cost of £537,354, 62 patients in 2009 at a cost of £311,364, and 75 patients in 2010 at a cost of £376,650. The budget impact analysis has not identified any direct savings with the use of Truvada® or influences on the uptake of other therapies. Indirect costs associated with Truvada® use are not incorporated.