All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Emtricitabine (Emtriva®)
Gilead Sciences Ltd

Advice No: 0407 - June 2007

Recommendation of AWMSG:

Emtricitabine (Emtriva®) is recommended for use within NHS Wales as an option for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines. It should only be prescribed by HIV specialists. AWMSG has requested the manufacturers make a further submission relating to paediatric use.

This report should be cited as:

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 (Emtriva®) is recommended for use within NHS Wales as an option for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines. It should only be prescribed by HIV specialists. AWMSG has requested the manufacturers make a further submission relating to paediatric use.

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 emtricitabine in patients who had previously received other treatments. The evidence submitted by the manufacturers did not include data in children although such use is within the licenced indications.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Treatment of HIV-1 infected adults and children in combination with other antiretrovirals. This indication is based on studies in treatment naïve patients and treatment experienced patients with stable virological control[1,2].

2.2 Dosing:
Adults: One 200mg hard capsule, taken orally, once daily or 24ml of 10mg/ml oral solution (240mg) once daily[1,2].
Children and adolescents up to 18 years of age: For children weighing at least 33kg and able to swallow hard capsules the hard capsule dose is the same as the adult dose[1]. Alternatively the oral solution may be given at a dose of 6mg/kg body weight up to a maximum of 240mg (24ml) once daily[2].

2.3 Market authorisation date: 24th October 2003[3]

2.4 UK Launch date: launched 2003

3.0 DECISION CONTEXT

This assessment aims to review the evidence submitted by the company on the clinical and cost effectiveness of Emtriva® (emtricitabine) in the treatment of HIV-1 infected patients.

Current UK guidance (in adults) 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. Didanosine in combination with lamivudine or emtricitabine are well tolerated and effective combinations of NRTIs. 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) though long-term data on toxicity and resistance development are currently lacking for these products [4,5].

For children infected with HIV, the choice of initial therapy is less certain according to the 2004 Paediatric European Network for the Treatment of AIDS (PENTA) guidelines[6]. In a bid to address this, a collaborative study by PENTA and the Paediatric and AIDS Clinical Trials Group is underway. In the PENPACT1 trial children are randomly assigned to receive a PI or an NNRTI in addition to two NRTIs as triple antiretroviral therapy (see section 9.1)[7].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company have based their submission on three clinical trials, two Phase III open label comparative studies evaluating the use of emtricitabine in combination with tenofovir DF (plus an NNRT or boosted PIs) and one double-blind study in combination with didanosine and efavirenz. All studies presented were in treatment-naïve adults.

Two of the three studies provide evidence of the clinical efficacy and safety of emtricitabine when used in combination with tenofovir DF and can be found in the Truvada® appraisal report (AWMSG no: 0507). The third study provides evidence of improved safety and efficacy for emtricitabine when compared with stavudine on a background treatment of didanosine and efavirenz. The probability of persistent virological response was higher in those patients receiving emtricitabine-based therapy at week 24, 48 and 60. The improved response with emtricitabine prompted a change in protocol allowing patients to switch to open-label emtricitabine.

Evidence has not been presented for the clinical efficacy of emtricitabine in the treatment of HIV-I infected children (below 18 years of age).

The trial data included in the company submission supports the clinical effectiveness of emtricitabine when used in combination with tenofovir DF or didanosine (plus an NNRTI or boosted PI). Emtricitabine has not been assessed in combination with alternative NRTIs.

It is the opinion of the committee that the clinical evidence presented by the company indicates that Emtriva® 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 submission included a cost-utility model that compared an emtricitabine/tenofovir regimen against a zidovudine/lamivudine regimen. A Markov model was constructed that described 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:

Evidence for the safety and efficacy of emtricitabine in children under the age of 18 years of age has not been demonstrated in this submission.

The company submission has predominantly focused on the clinical and cost effectiveness of emtricitabine when used in combination with tenofovir DF. The efficacy of emtricitabine in combination with alternative NRTIs is limited and requires further evaluation.

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

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company have submitted three trials as evidence for the clinical effectiveness of emtricitabine[8-13]. The first two trials are Phase III open label studies where emtricitabine was used in combination with tenofovir DF (study 934 and 418)[9-12]. The third trial was double-blinded and assessed the use of emtricitabine in combination with didanosine and efavirenz (study 301A)[13]. All studies were in adults and all patients were antiretroviral-naïve.

These studies have also been submitted as evidence for the therapeutic appraisal of Truvada® (emtricitabine and tenofovir DF). Studies 934 and 418 have been summarised in the Truvada® assessment report (No. 0507).

6.1.1 Emtricitabine, didanosine and efavirenz versus stavudine, didanosine and efavirenz (Study FTC-301A)[13]

This randomised double-blind double-dummy study was designed to assess the safety and efficacy of emtricitabine compared with stavudine. Patients received either 200mg/day of emtricitabine (n=286) or 200mg stavudine twice daily (n=285), with a background treatment (open-label) of 400mg/day didanosine and 600mg/day efavirenz.

The primary endpoint of the study was achieving and maintaining plasma HIV RNA levels at or below the limit of assay quantification (≤400 or 50 copies/ml) at 48 weeks. Interim analysis was performed at 24 weeks and at a median follow up of 60 weeks. This end point followed the FDA TLOVR algorithm[14]. Secondary end points included virological failure, change from baseline in absolute CD4 cell count, genotypic resistance and incidence of treatment-limiting adverse events. The probabilities of persistent virological response, of virological failure and of developing a treatment-related adverse event were analysed using Kaplan-Meier methods.

At the week 24 analysis the independent data and safety monitoring board (DSMB) recommended that the double-blind comparative phase be terminated and all patients demonstrating lesser response be allowed access to the group demonstrating greater response. The median double-blind follow-up at this point was 42 weeks. Patients were able to receive open-label emtricitabine or continue receiving blinded therapy until the last randomised patient completed week 48. Four patients (<1%) completed the week 48 visit after switching to open label emtricitabine. By the time the protocol had been amended many individuals had reached the week 48 visit. The median duration of double-blind follow up was 60 weeks by the time the last patient had completed the week 48 visit.

Results:
Eight-one percent (232/286) of the emtricitabine group and 68% (193/285) of the stavudine group completed 48 weeks of therapy. The probability of persistent virological response over the 60 weeks are included in table one.

	Emtricitabine group (n=286)	Stavudine group (n=285)	P value
Week 24			
≤ 50 copies/ml	85%	76%	0.005
≤ 400 copies/ml	88%	81%	0.03
Week 48			
≤ 50 copies/ml	78%	59%	<0.001
≤ 400 copies/ml	81%	68%	<0.001
Week 60			
≤ 50 copies/ml	76%	54%	<0.001
≤ 400 copies/ml	79%	63%	<0.001

Table 1. Probability of persistent virological response at the 50 & 400 copies/ml thresholds (ITT population)

As expected, response rates were higher for patients with baseline viral loads less than or equal to 100,000 copies/ml across treatment groups.

The probability of virological failure was 4% in the emtricitabine group and 12% in the stavudine group (P<0.001).

Mean increases from baseline in absolute CD4 cell counts did not differ significantly between the two treatment groups (P=0.15) at week 48. There was no difference in adherence to study medication between groups.

Point to note:

- The mean baseline CD4 cell count was higher than the (median) count observed in study 934. The overall range was wide.

6.2 Safety:
The assessment of safety in the emtricitabine/tenofovir DF versus zidovudine/lamivudine comparative study (Study 934) at week 96 comprised of 511 patients who had received any study medications[10]. Grade II to IV adverse events, in accordance with the modified Common Toxicity Criteria, were comparable between groups, 182/257 (72%) patients in the emtricitabine/tenofovir DF group versus 180/254 (71%) in the zidovudine/lamivudine group. No significant difference in the rate of laboratory abnormalities was observed between groups. 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[9]. No patient discontinued treatment because of anaemia from weeks 48 through 96[10].

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 the 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 to 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 and stavudine[9,10,13]. Among the patients who had dual energy x-ray absorptiometry (DEXA) scans at week 48 and 96 of study 934, 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) [8]. 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[4].

In study FTC-301A, lipodystrophy was reported in 17 (6%) patients receiving stavudine compared with one (<1%) patient receiving emtricitabine, this difference was statistically significant (P<0.05)[13]. Due to the risk of lipoatrophy (and peripheral neuropathy) stavudine is not recommended for initial therapy in treatment-naïve patients[4].

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)[10]. 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[11,12]. This is a common side effect associated with protease inhibitors but may also be associated with the use of Emtriva®[1,2].

In the FTC-301A study (emtricitabine versus stavudine) treatment emergent serious adverse events did not differ between groups. However diarrhoea, nausea, lipodystrophy (investigator assessed), abnormal dreams, neuropathy, paraesthesia and increased cough were statistically significantly more frequent in the stavudine treated group (P<0.05)[13].

Skin discolourations, manifesting as hyperpigmentation on the palms and/or soles, occurred in more patients treated with emtricitabine compared to stavudine (3% versus <1%, P<0.05) [10]. Hyperpigmentation was also 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[9].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

The company have listed lamivudine (Epivir®) as the main comparator to emtricitabine (Emtriva®). Lamivudine in combination with zidovudine (plus efavirenz) has been compared with emtricitabine when used in combination with tenofovir DF (plus efavirenz) in an open-label study (study 934), further details of which can be found in the Truvada® assessment report advice no. 0507.

Currently there are seven NRTIs on the UK market available alone or in combination[15].

7.2 Comparative effectiveness:

The main comparator studies are included in the clinical effectiveness section of this report, section 6.1.1 and section 6.1.1 of the Truvada® assessment report, advice no. 0507. Comparative safety issues have been discussed under section 6.2. Comparative effectiveness issues in relation to adherence, quality of life and resistance are discussed under this section.

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 Emtriva® is taken once daily this has perceived benefits regarding adherence over twice daily regimens. However In study 934 by week 96 adherence, as measured by pill counts, did not differ significantly between treatment groups[10]. 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.

Quality of life:

There are no data included in the submitted trials assessing quality of life. 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. Simply stating that treatment with emtricitabine 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 which 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[4,5].

In study 934, genotypic data were collected at week 48 on 35 patients who met the criteria for resistance analyses[9]. 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 [10]. 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[12].

In study FTC-301A, genotypic analysis was performed on 13 patients in the emtricitabine group and 35 of 37 patients in the stavudine group with virological failure. Virological failure with at least one new genotypic mutation developed in a greater proportion of patients in the stavudine group (11%) versus the emtricitabine group (4%), P=0.005[13]. Mutations associated with NNRTI resistance were the most commonly reported.

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[8].

However, in line with the licensed indication, Emtriva® has not been studied in patients who are failing their current regimen or who have failed multiple regimens[1,2].

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 emtricitabine over relevant comparators justify the additional costs, and if so,
2. whether the total budgetary impact of supporting the use of emtricitabine 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 emtricitabine.

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 co-formulated product (Truvada®).

8.3.1 Summary of the evidence:

The company submission included a cost-utility model that compared an emtricitabine/tenofovir 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 non-nucleoside reverse transcriptase inhibitor (such as efavirenz) or boosted protease inhibitor 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 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 *plus efavirenz* compared with zidovudine /lamivudine *plus efavirenz*. Therefore, the model uses triple therapy-derived transition probabilities for the emtricitabine/tenofovir 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 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 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 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 regimen vs. 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 regimen compared with the zidovudine /lamivudine regimen was £14,806. The incremental cost per QALY was £18,229. This was based on emtricitabine/tenofovir 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.

Emtricitabine is available as a single agent (Emtriva®) and as a component of a combination product (emtricitabine + tenofovir, Truvada®). The budget impact analysis assumes limited prescribing of the single agent. Based on market share estimates and commercial data for 2006 (company data on file), the budget impact analysis claims that only 5 patients would receive the single emtricitabine product in each year up to 2010. Based on BNF list prices[15], the annual cost of emtricitabine alone would be £1,962 per patient. Therefore, for 5 patients the acquisition cost to NHS Wales would be £9,810 per year. The budget impact analysis has not identified any direct savings with the use of emtricitabine or influences on the uptake of other therapies. Indirect costs associated with emtricitabine use are not incorporated.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Emtricitabine, in combination with a second NRTI and an NNRTI would be considered a first-line treatment option for adult patients with HIV infection in whom treatment is indicated[3].
- In 2004, European guidance recommended that prescribers enter their paediatric patients onto the PENPACT1 collaborative trial[6,7]. This trial is now in follow up, further information on this can be found at: www.ctu.mrc.ac.uk/penta/trials.htm#infollowup
- The 2004 PENTA guidelines for the use of antiretroviral therapy in paediatric HIV infection are due to be updated this year (2007)[6].
- 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].
- Emtriva® 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[3].

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

1. Summary of Product Characteristics. Emtriva® 200mg hard capsules. Available at http://emc.medicines.org.uk/ (accessed February 2007).
2. Summary of Product Characteristics. Emtriva® 10mg/ml oral solution. Available at http://emc.medicines.org.uk/ (accessed February 2007).
3. Form A: Initial appraisal information. Gilead Sciences Ltd. October 2006.
4. Gazzard B, Bernard AJ, Boffito M et al. British HIV Association (BHIVA) Guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). HIV Med 2006;7 (8):487-503.
5. Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005). Available at http://www.bhiva.org/guidelines/2005/HIV/guidelines2005.pdf (accessed February 2007).
6. Paediatric European Network for Treatment of AIDS (PENTA). 2004 PENTA Guidelines for the use of antiretroviral therapy in paediatric HIV infection. Available at http://www.ctu.mrc.ac.uk/penta/guidelines.htm (accessed March 2007).
7. Paediatric European Network for Treatment of AIDS (PENTA). PENTA Trials. Available at http://www.ctu.mrc.ac.uk/penta/trials.htm (accessed March 2007).
8. Form B: Detailed appraisal information. Gilead Sciences Ltd. January 2007.
9. Gallant JE, DeJesus E, Arribas JR et al. Tenofovir DF, emtricitabine and efavirenz vs. zidovudine, lamivudine and efavirenz for HIV. N Engl J Med 2006;354:251-60.
10. Pozniak AL, Gallant JE, DeJesus E et al. Tenofovir disoproxil fumarate, emtricitabine and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naïve patients: virologic, immunologic and morphologic changes: a 96 week analysis. J Acquir Immune Defic Syndr 2006; 43(5):535-40.
11. Gathe J, Podzamczer D, Johnson M et al. Once-daily vs. twice-daily lopinavir/ritonavir in antiretroviral-naïve patients: 48 week results. 11th Conference on Retrovirus and Opportunistic Infections, San Francisco, CA, February 8th-11th 2004. Poster 570.
12. Molina JM, Wilkin A, Domingo P. Once daily vs. twice daily lopinavir/ritonavir in antiretroviral-naïve patients: 96-week results. 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, 24-27th July 2005. Poster WePe12.3C12.
13. Saag MS, Cahn P, Raffi F et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. JAMA 2004; 292 (2): 180-90.
14. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: considerations for accelerated and traditional appraisal. October 2002. Available at http://www.fda.gov/cder/guidance/3647fnl.pdf (accessed March 2007).
15. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. 53rd edition. London: Pharmaceutical Press. 2007.
16. National Public Health Service for Wales. HIV/AIDS: Surveillance data. http://www2.nphs.wales.nhs.uk/icds/page.cfm?pid=520 (accessed March 2007).
17. All Wales Medicines Strategy Group. Ministerial recommendation. Enfurvirtide (Fuzeon®) May 2004. Available at http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=371&id=44087&pid=98995 (accessed February 2007).
18. Gay Men's Health Crisis. Available at http://www.gmhc.org/health/glossary3.html (accessed March 2007)

19. Chancellor JV, Hill AM, Sabin CA et al. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. Pharmacoeconomics 1997;12 (1): 54-66.
20. Trueman P, Youle M, Sabin CA et al. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. HIV Clin Trials 2000; 1 (1): 27-35.
21. Petrou S, Dooley M, Whitaker L, et al. Cost and utilisation of community services for people with HIV in London. Health Trends 1995; 27: 62-8.
22. Health Protection Agency's Centre for Infections. The Survey of Prevalent HIV Infection Diagnosed (SOPHID). National data for 2004; September 2005.
23. Health Protection Agency for Infections, Health Protection Scotland, Institute of Child Health. AIDS/HIV Quarterly Surveillance Tables. Cumulative UK data to end March 2006; April 2006.

APPENDIX 1

Additional Clinical Information

The British HIV Association (BHIVA 2005)[5] recommends commencing treatment in adults 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 Paediatric European Network for Treatment of AIDS (PENTA 2004) recommends commencing treatment in children and infants when the risk of progression is 'significant'. Consensus on the definition of 'significant' is unclear, however individual risk levels can be calculated based on a child's current age, CD4 percentage and viral load. Further information regarding this can be found at www.pentatrials.org and www.etu.mrc.ac.uk/penta/guideline.pdf. New guidelines are due to be produced in 2007[6].

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.

Company submission - economic evidence

1. Description of company submission

The company submission included a cost-utility model that compared an emtricitabine/tenofovir regimen against a zidovudine/lamivudine regimen[8]. A Markov model based on that constructed by Chancellor et al 1997 was employed[19]. 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 6.1.1 of Truvada® assessment report advice no. 0507)[9,10]. 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. Emtricitabine is licensed for use in children[1,2], but this study and cost-effectiveness analysis is not 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 with the current standard nucleoside backbone of zidovudine/lamivudine. This is an appropriate dual nucleoside

analogue comparator as indicated by recent British HIV guidelines[4]. However, the guidelines also state that treatment should also include either a non-nucleoside reverse transcriptase inhibitor or boosted protease inhibitor. 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 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[20]. 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 a non-nucleoside reverse transcriptase inhibitor (such as efavirenz) or a boosted protease inhibitor in addition to their dual nucleoside analogue therapy.

For the emtricitabine/tenofovir 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)[20] using the relative risk of treatment failure (defined as a HIV-1 RNA viral load >400copies/ml at week 48) with emtricitabine/tenofovir *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 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 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 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[19,20]. 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 2 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[20]. 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 regimen vs. 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 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[21]. 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 persisted for two years, the incremental cost per life year gained with the emtricitabine/tenofovir regimen compared with the zidovudine/lamivudine regimen was £14,806. The incremental cost per QALY was £18,229. This was based on emtricitabine/tenofovir 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, 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, 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 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)[22,23]. 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 <350. 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.

Emtricitabine is available as a single agent (Emtriva®) and as a component of a combination product (emtricitabine + tenofovir, Truvada®). The budget impact analysis assumes limited prescribing of the single agent. Based on market share estimates and commercial data for 2006 (company data on file), the budget impact analysis claims that only 5 patients would receive the single emtricitabine product in each year up to 2010. Based on BNF list prices[15], the annual cost of emtricitabine alone would be £1,962 per patient. Therefore, for 5 patients the acquisition cost to NHS Wales would be £9,810 per year. The budget impact analysis has not identified any direct savings with the use of emtricitabine or influences on the uptake of other therapies. Indirect costs associated with emtricitabine use are not incorporated.