Review of applications for:
1) emtricitabine
2) tenofovir
3) emtricitabine and tenofovir fixed dose combination
for inclusion on the WHO Model List of Essential Medicines.

Background

Gilead Sciences Incorporated has applied to have three new products for the treatment of HIV/AIDS added to the WHO Model List of Essential Medicines:
- emtricitabine 200mg capsules
- tenofovir 300mg tablets
- emtricitabine 200mg plus tenofovir 300mg as a fixed dose combination tablet.

*Emtricitabine* is being proposed as an example of the therapeutic class of HIV nucleoside analogue reverse transcriptase inhibitors. *Tenofovir* is similarly being proposed as an example of HIV nucleoside/nucleotide analogue reverse transcriptase inhibitors. The fixed dose combination product is being proposed a combination to be used with another antiretroviral drug (ARVs) as a way of enhancing adherence to therapy and meeting the policy aims of supplying ARVs as fixed dose combination products.

The Model EML currently lists 12 ARVs:
- 4 nucleoside reverse transcriptase inhibitors – abacavir, didanosine (ddl), lamivudine (3TC), stavudine (d4T) and zidovudine (AZT or ZDT)
- 2 non-nucleoside reverse transcriptase inhibitors – efavirenz and nevirapine
- 5 protease inhibitors – indinavir, lopinavir + ritonavir, nelfinavir, ritonavir alone and saquinavir.

The WHO treatment guidelines for HIV are:
“WHO recommends that in resource-limited settings a single first-line regimen should be identified for the treatment of the majority of new patients. This regimen would consist of 2 nucleoside analogs and either a non-nucleoside or abacavir, or a protease inhibitor. Zidovudine (ZDV)/3TC is the initial recommendation for a dual nucleoside analog with d4T/3TC, ZDV/ddI and ddI/3TC as possible alternatives. Efavirenz and nevirapine are recommended non-nucleosides, while recommended protease inhibitors include ritonavir-boosted PIs (indinavir, lopinavir, saquinavir) or nelfinavir. A second line regimen should be chosen to substitute first line regimens when needed (for toxicity or treatment failure).”

In addition, there has been considerable support of the development of FDCs, as noted above, as a way of enhancing provision of effective antiretrovirals to communities generally. The WHO pre qualification project website ([http://mednet3.who.int/prequal/](http://mednet3.who.int/prequal/), accessed on Jan 4 2005) lists the following combinations as of interest for applications:
- Lamivudine + Stavudine
• Lamivudine + Zidovudine
• Lamivudine + Stavudine + Efavirenz
• Lamivudine + Stavudine + Nevirapine
• Lamivudine + Zidovudine + Efavirenz
• Lamivudine + Zidovudine + Nevirapine

Currently there are products pre-qualified for the combination of Lamivudine + Stavudine + Nevirapine as well as a number of others (eg. Lamivudine + Stavudine + abacavir).

Evidence submitted in support of the applications

All applications were submitted by the manufacturer. As these products are relatively new on the market internationally (emtricitabine was approved in 2003 by the USA and EU and the combination product was approved in 2004 by the USA) there are few published studies. Most of the data provided were based on unpublished study reports from the sponsor or papers available in abstract only. There are no published systematic reviews of these drugs.

1. Emtricitabine

Emtricitabine is structurally similar to lamivudine. The recommended dose in adults is 200mg/day; in children, the recommended dose is 6mg/kg up to a maximum of 240mg/day, given as 10mg/mL oral solution.

The data presented in the application are primarily the sponsor’s summaries of the regulatory trials. Most are cited as poster publications only and the posters/abstracts were not provided so there is no way of independently verifying the data. The results of the main trial used to support the regulatory approval of the product in the US were published as Saag et al in 2004 (JAMA, 292:180-190.) An independent literature search carried out during the course of this review found one additional published paper, Molina et al, HIV Medicine, 2004;5:99-104. This trial is reported as a substudy of the ANRS 091 trial and concentrates on the pharmacokinetics of emtricitabine and may be a duplicate publication of Molina et al, 2000.

The published study, Saag et al, was a randomised double blind controlled trial carried out in 571 adult ARV-naïve patients. It was designed to compare emtricitabine (plus didanosine and efavirenz) with stavudine (with the same combination). The study was carried out in 101 research clinics in North America, Latin America and Europe. Of relevance for the EDL Committee is (1) that there were no study centres in Africa or South East Asia, and although approximately 50% of the study population was non-white, less than 2% were Asian and less than 20% were black; and (2) the study did not include subjects younger than 18 years, although the product is being proposed for use in children.

The subjects were treated with the single daily dose regimen for 48 weeks. The primary endpoint in the trial was virological response, which is now generally accepted as an adequate surrogate measure for clinical endpoints.
such as death or AIDS defining illness. There were several secondary endpoints, including CD4 cell count, disease progression, adverse events and laboratory abnormalities.

A planned interim analysis of the trial was carried out when all patients had completed at least 24 weeks of treatment. At this analysis, the patients treated with emtricitabine combination had a higher probability of virological response, 85% vs 76% in the stavudine group and the independent safety monitoring committee recommended that open-label emtricitabine be offered. The difference between the two treatments persisted at 48 week (78% vs 59%) and at 60 weeks (76% vs 54%). Adherence to treatment was not statistically significant between the two groups.

Adverse events again generally favoured emtricitabine. Pancreatitis and lactic acidosis were not reported in the emtricitabine group and were reported in the stavudine group. Lipodystrophy was more frequent in the stavudine group as were laboratory abnormalities. Overall, the authors of the study reasonably conclude that the results appear to suggest that emtricitabine is superior to stavudine both in terms of efficacy and safety.

The limitation of this application is that none of the other studies can be fully reviewed apart from the recent pharmacokinetic study (Molina, 2004). Further, the application does not explain the outcome from the study (FTC-302) in South Africa that was stopped in 2000 due to a possible excess of deaths (BMJ, 2000) and this study although referred to in the text of the information is not listed in the Attachment. Based on the table of trials provided in the application, it would appear that there are data for effectiveness and safety in approximately 620 patients overall (excluding the ALIZE trial as the sample size of this study is not stated). Arguably, this number of patients is only just sufficient for regulatory purposes, and it certainly does not provide a sufficient population base to estimate the likelihood of rare but serious adverse events. The population exposure claimed in the application of 10,395 subjects cannot be substantiated.

As noted above, an important population for the context of this application is the paediatric group; there is one early report of an unpublished study of what appears to 37 patients as the basis for trying to determine effectiveness and safety in subjects between ages 3-21 years.

It is therefore difficult to make an independent assessment of the safety and effectiveness of this product compared to other available treatments.

**Recommendation**

The application should be rejected. There are insufficient publicly available data to allow an independent assessment of comparative effectiveness and safety, and in particular, there appear to be no studies yet complete in highly relevant populations likely to use the product should it be listed on the Model EML.
**References**


2. **Tenofovir DF**

Tenofovir disopoxil fumarate is being proposed for addition to the EML as an example of the therapeutic class of HIV nucleotide reverse transcriptase inhibitors. It is available as a 300mg tablet, and is given as a single daily dose. The application notes that there are as yet no data for its use in children under 18 years of age.

As with the application for emtricitabine, the data provided in the application are generally the sponsor’s summaries of the unpublished study reports that were used as the basis of the regulatory review in the US. References were not provided with the application and most cited are posters. An independent literature search carried out for this review identified several reports published over the last year which appear to include relevant information not provided in the application, including case reports in relation to renal toxicity, a systematic review of the use of tenofovir in children and at least 2 observational studies of adverse effects and interactions.

The published version of the key trial was retrieved during the evaluation (Gallant et al, *JAMA*, 2004). This was a randomised double blind study of 753 adult treatment naïve patients conducted in 81 centres in the US, South America and Europe over the period 2000 to January 2004. The treatments were tenofovir DF (n=299) or stavudine (n=303) in combination with lamivudine and efavirenz. The primary outcome of the trial was the proportion of patients with HIV RNA levels of less than 400 copies/ml at week 48 of treatment.

This trial was designed as an equivalence study, and the pre-determined criteria for equivalence was a difference in viral load of < -10%. At week 48, the proportion of patients with a viral load of < 400 copies/ml was 80% in the tenofovir group and 84% in the stavudine group, with the 95% confidence interval for the difference of -10.4% to 1.5%. This exceeded the
predetermined criteria for equivalence and on the basis of this outcome, stavudine was superior. However, analysis of secondary outcomes in the trial did meet the pre-determined equivalence criteria.

The conclusion from the trial was that tenofovir in combination was effective and appeared to be safer than stavudine. Subsequent studies have not attempted to clarify which treatment is superior but there have been a number of issues raised about safety. Firstly, there appears to be a risk of renal adverse events associated with tenofovir. In addition DDI toxicity has been reported when used in combination when tenofovir, though this appears to be reduced by reduction in ddI doses. Finally, pancreatitis has also been reported as a serious adverse effect.

The second major study of tenofovir (Study 907) has also been published as Squires et al, 2003. This study was a randomised controlled trial in 552 patients already receiving ARVs who had a degree of resistance to treatment. At 24 weeks, patients in the tenofovir group had a significantly greater decrease in viral load than those in the placebo group, so that all patients were offered open label tenofovir. There were no significant safety concerns in this study.

Internationally, tenofovir has been available since 2001. It has apparently been used in a number of developing countries but details of the use in these settings were not provided in the application. The two major studies described above did not include subjects from Africa or South East Asia. As noted in the application, there is no data to support use in children. Total patient exposure to date is said in the application to be over 10000 patients.

The major concern would therefore appear to be the risk of renal toxicity with the drug. It is difficult to assess exactly how much of a problem this is in the absence of a comprehensive independent review of the safety of tenofovir to date, which is not provided in the application. It is not clear how much monitoring would be required in resource poor settings to manage this effectively, and it is not clear how this compares with the renal toxicity of the other currently listed ARVs. Advice should be provided from the appropriate Cluster in WHO regarding the experience of renal toxicity with ARVs in resource poor settings to date.

**Recommendation**

The Model EML Committee should seek advice regarding the management of potential renal toxicity in resource poor settings. If this can be adequately addressed, tenofovir could be added to the Model EDL.

**References**

1. From literature search, limited to 2004 - current.

Therapy regimens is not observed more frequently: A cohort and case-control study.


Kakuda TN, Anderson PL, Becker SL. CD4 cell decline with didanosine and tenofovir and failure of triple nucleoside/nucleotide regimens may be related. AIDS. 2004;18:2442-4.


2. Major clinical trials.


3. Emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablets

The third application from Gilead is for a fixed dose combination preparation tablet containing emtricitabine 200mg and tenofovir disoproxil fumarate 300mg (proprietary name, Truvada). As noted above, this is in response to the general policy of trying to increase the number of FDC products that are available for HIV, to maximize adherence. The product, Truvada, was registered in the US in August 2004.

The data in the application are a summary of clinical trials submitted to the USA FDA for registration. There are no published versions of these studies; they are only available as posters from meetings and therefore it is not possible to independently evaluate the information. It is also not clear from the application what studies actually used the FDC preparation. An independent literature search carried out during this review could not identify any published studies of eth product that is proposed for addition to the EML.

The summary of safety information provided in the application states that ‘238 patients have received combination therapy either tenofovir DF and emtricitabine with either a NNRTA or PI for 24 to 48 weeks.’ Again it is not clear whether this is with the FDC or with the components individually.
Recommendation

In principle, this fixed dose combination may be a reasonable proposal. However, the data supplied do not allow the Committee to make a judgment on comparative effectiveness and safety, nor whether there are even bioequivalence data to support the FDC being the same as the two components given separately which was presumably required as the minimum information by the US FDA. The application is premature and should be rejected.

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