Scottish Medicines Consortium

Resubmission

emtricitabine 200 mg hard capsules (Emtriva®) **No. 105/04**

Gilead Sciences International

6 January 2006

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

ADVICE: following a resubmission

Emtricitabine (Emtriva®) is accepted for use within NHS Scotland for the treatment of HIV-1 infected adults in combination with other antiretroviral agents. It should be prescribed only by HIV specialists.

This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control in whom, as part of antiretroviral therapy (ART) regimens, it has shown virological responses comparable with other ART. There is no experience of use in patients who are failing their current regimen or who have failed multiple regimens.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Emtricitabine, 200 mg, capsules (Emtriva®)

Indication

Treatment of HIV-1 infected adults in combination with other antiretroviral agents.

This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control. There is no experience of use in patients who are failing their current regimen or who have failed multiple regimens.

Dosing information

The recommended dose for adults is 200 mg once daily.

UK launch date

1st December 2003

Comparator medications

Cost of relevant comparators

The adult dose regimens and annual costs for solid oral dose formulations of NRTIs licensed in the UK are detailed in the table.

Product	Regimen	Cost / 52 weeks (£)
Emtricitabine 200mg	**200mg daily**	**1984**
Tenofovir disoproxil as fumarate 245 mg	245mg daily	3094
Abacavir tabs 300 mg	600mg daily in 1-2 doses	2691
Zidovudine 100 mg and 250 mg	500-600mg daily in 2-3 doses	2020-2424
Stavudine 30 mg and 40 mg	30-40mg twice daily	2018-2079
Didanosine 200 mg	250-400 mg daily in 1-2 doses	1316-1986
Lamivudine 150 mg	300mg daily in 1-2 doses	1846 - 2029
Zalcitabine 750 mcg	750mcg three times daily	1539

The adult dose regimens and annual costs for 2-NRTI combination products marketed in the UK are given below.

Product	Regimen	Cost / 52 weeks (£)
Emtricitabine / tenofovir DF 200mg/300mg	**One daily**	**5078**
Abacavir / lamivudine 600/300 mg	One daily	4537
Zidovudine / lamivudine 300 mg/ 150 mg	One twice daily	3866

Summary of evidence on comparative efficacy

Emtricitabine is an antiretroviral drug belonging to the nucleoside reverse transcriptase inhibitors (NRTI) which inhibit viral replication.

The primary end-point in all the studies described in this assessment has been the proportion of patients achieving and maintaining viral load (HIV-1 RNA) at or below a limit of quantification (LOQ) pre-specified as either 400 copies/ml or 50 copies/ml. In some cases this has involved an intention-to-treat (ITT) population modified according to an algorithm from the American Food and Drugs Administration (FDA) for the time to loss of virological response (TLVOR) which censors missing data and counts patients with discontinuation or loss to follow-up as failures (NC=F).

Emtricitabine in antiretroviral treatment (ART)-naïve patients

Emtricitabine 200 mg once daily was compared with stavudine 40 mg twice daily (30 mg if weight <60 kg), each with a once-daily background regimen of didanosine and efavirenz, in a double-blind randomised controlled trial involving an intention to treat (ITT) population of 286 and 285 respectively. Adult patients were included if they had a viral load at screening of ≥5000 copies/ml and excluded if they had severe haematological, hepatic or pancreatic abnormalities at baseline. Randomisation was stratified according to viral load and geographical location.

The primary end-point was a persistent virological response, and the published paper reports the proportion of patients achieving this end-point for a LOQ of both 50 and 400 copies/ml. The probabilities of persistent response/failure were estimated using Kaplan-Meier methods with a 2-sided log rank test at a significance level of 0.05 (NC=F).

At 24 weeks the probability of patients achieving the primary end-point at the quantification limit of 50 copies/ml was 85% (n=286) for the emtricitabine group compared with 76% (n=285) for the stavudine-treated group, p=0.005. This was maintained with an analysis performed at a median follow-up of 60 weeks, though at a slightly lower level (76% vs 54%, p<0.001). Results were similar for a quantification limit of 400 copies/ml with a response rate at 60 weeks of 79% vs 63%, p<0.001.

Emtricitabine as a fixed-dose combination with another NRTI, tenofovir disoproxil fumarate, equivalent to a once-daily dose of 200 mg/300 mg is being compared to an NRTI combination of lamivudine and zidovudine 150/300 mg twice daily in an ongoing study in the treatment of HIV-1 infection in adult ART-naïve patients. Both groups are given a background regimen of efavirenz 600 mg daily. Inclusion criteria include HIV-1 RNA >10,000 copies/ml and creatinine clearance ≥50 ml/minute.

In interim analyses, the primary end-point for a modified intention to treat population (who followed the FDA LOVR algorithm) was non-inferiority of emtricitabine/tenofovir compared with the comparator arm in maintaining viral load ≤ 400 copies/ml, which would be concluded if the lower bound of the confidence intervals for the difference in the proportion of responders in the FDA LOVR algorithm exceeded -13%. Emtricitabine/tenofovir showed superior antiviral efficacy to lamivudine/zidovudine both at 24 weeks and at 48 weeks. Response rates at 48 weeks were 177/243 (73%) for lamivudine/zidovudine and 206/244 (84%) for emtricitabine/tenofovir, p=0.002, 95% confidence intervals for the difference 4.3%, 18.6%. This represented a slight decrease in response rates from 24 weeks which were 88% vs 80% with a difference of 7%: (95% CI 1%, 13%).

In another trial with ART-naïve patients, emtricitabine/tenofovir provided the background regimen for a comparison of once-daily and twice-daily dosing with ritonavir-boosted lopinavir. The proportion of patients maintaining a viral load ≤50 copies/ml was 64%-70% at 48 weeks and 53-57% at 96 weeks.

Emtricitabine in antiretroviral treatment experienced patients

Patients in this Phase III open-label study were required to have a stable viral load <400 copies/ml at screening; and ≥12 weeks on a stable triple antiretroviral regimen containing lamivudine, an NRTI (stavudine or zidovudine) and a marketed PI or NNRTI.

They were randomised (2:1) to replacement of lamivudine 150 mg twice daily with emtricitabine 200 mg daily or to continuation with the existing lamivudine regimen. The primary efficacy end-point was durable suppression of plasma HIV-1 RNA levels ≤ 400 copies/ml through 48 weeks of the study (NC=F). This was a non-inferiority study based on a 15% limit in the difference in proportions of responders with ≤400 copies/ml at week 48.

The proportion of responders at 48 weeks was lower for the emtricitabine group than for the group continued on lamivudine (73% vs 82%), representing a stratum-adjusted difference of -5.8%, and 95% CI for the difference (-13.5%, 1.8%) which met criteria for non-inferiority of the emtricitabine group over comparator.

The trials above varied according to whether the primary analysis was based on a limit of detection for viral load of 50 copies/ml or 400 copies/ml,. However, results were reported as a secondary end-point for the alternative threshold in each case. Secondary end-points also included rates of virological and efficacy failure and a measure of change for the CD4+ cell count. In general, the direction of benefit for these secondary end-points was in the same direction as in the primary analysis for each trial.

Resistance to emtricitabine is associated with a change in the amino acid at codon 184 of the HIV reverse transcriptase enzyme from methionine to valine, called the M184V mutation. This has occurred in vitro and in HIV-1 infected patients. Emtricitabine-resistant viruses are cross-resistant to lamivudine, but retain sensitivity to other NRTIs (e.g. zidovudine, abacavir, stavudine, tenofovir, didanosine and zalcitabine), all NNRTIs and all PIs. Viruses which are resistant to NNRTIs and the NRTIs, zidovudine, zalcitabine and didanosine, retain sensitivity to emtricitabine.

Patients who completed 48 weeks in the study above with viral load ≤400 copies/ml could continue receiving emtricitabine in a rollover study. At four years, the Kaplan-Meier probability of virological failure, based on maintenance of virological suppression below 400 copies/ml, was 11% with no significant difference between those assigned to emtricitabine or lamivudine in the original double-blind study.

Summary of evidence on comparative safety

Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported with NRTIs and caution is advised when treating patients with risk factors for liver disease.

Emtricitabine is principally eliminated by the kidney, via glomerular filtration and active tubular secretion. Caution is advised when it is co-administered with drugs which are also eliminated by active tubular secretion, as increases in serum concentrations of either drug may result.

In a pooled analysis of three studies comparing emtricitabine to stavudine or lamivudine in addition to background regimens of ART, the proportion of patients reporting at least one treatment-related adverse event was 510/814 (63%) for emtricitabine and 429/665 (64%) for control regimens. The most common treatment-related adverse events in both groups with an incidence ≥5% in the emtricitabine group included diarrhoea, headache, nausea, dizziness, abdominal pain, asthenia, rash and vomiting, with small differences between groups generally favouring emtricitabine.

In a comparison of a fixed dose combination of emtricitabine and tenofovir DF vs a combination of lamivudine/zidovudine with a background of efavirenz in both groups the incidence of treatment-related adverse events was 76/257 (30%) vs 115/254 (45%) respectively. The adverse event profile was similar to the above and the few differences in incidence were generally in favour of the emtricitabine/tenofovir arm. For example, nausea occurred in 11% vs 25% of patients respectively and anaemia was reported in 6% of patients assigned to lamivudine/zidovudine but none in the emtricitabine/tenofovir DF group.

Summary of clinical effectiveness issues

In the first trial described, an interim analysis at 24 weeks demonstrated a greater response for emtricitabine-treated patients, and the protocol was altered to offer patients the option to continue with blinded treatment or switch to open-label emtricitabine. This change was implemented late in the trial when most patients had completed 48 weeks.

Stavudine is not currently one of the NRTIs recommended in British HIV Association (BHIVA) guidelines for initial treatment and it was the direct comparator for emtricitabine in the main trial in treatment-naïve patients. The significantly higher response rate observed with emtricitabine in the treatment-naïve study partly resulted from more discontinuations due to adverse effects in the group receiving stavudine in combination with didanosine.

The lower response rate with emtricitabine compared to lamivudine in the treatment-experienced study partly resulted from more discontinuations due to adverse effects in the emtricitabine group. As the study was open-label it is possible that patients receiving the new investigational drug were more aware of potential adverse effects than those continuing on their existing therapy. In practice the incidence of adverse effects with emtricitabine may not be greater than lamivudine.

The indication for emtricitabine is based on studies in treatment naïve patients and patients with stable virological control. There is no experience of use in patients who are failing their current regimen or who have failed multiple regimens.

The submission also presented efficacy data for tenofovir disoproxil fumarate which has previously been considered by the Scottish Medicines Consortium (SMC).

In current BHIVA guidelines, recommendations for treatment-naïve patients consist of a dual NRTI backbone with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI). They list six recommended NRTI (including emtricitabine and tenofovir DF) with no indication of preference for an individual agent.

In addition to the fixed dose combinations of emtricitabine/tenofovir DF and zidovudine/lamivudine compared in the trial discussed above, a combination of abacavir and lamivudine is available as a co-formulation and offers once-daily administration. There are no comparative data comparing this formulation or between abacavir and emtrictabine as individual agents. In support of the choice of comparator, the company submission states that zidovudine/lamivudine is the most widely prescribed 2-NRTI backbone in the United Kingdom.

Summary of comparative health economic evidence

A cost-utility analysis using a previously published Markov model structure was conducted comparing emtricitabine/tenofovir with zidovudine/lamivudine in treatment-naïve adults. The main data source was a clinical trial which compared these two groups. UK observational data were used to derive baseline transition probabilities for the zidovudine/lamivudine cohort to CD4 cell count health states, and relative risks applied to these for the emtricitabine/tenofovir cohort were derived from the trial. A 20 year time horizon was adopted.

The key results for the base case were:

- Estimated incremental cost per QALY gained v zidovudine/lamivudine of £19,602
- Estimated incremental cost per life year gained v zidovudine/lamivudine of £15,721

These results are based on an estimated incremental gain of 0.61 life years per patient at an incremental cost of £9,590. Sensitivity analysis indicated the results were most sensitive to the discount rate used, starting health state and the relative risk statistic for treatment effect. However, the ICERs remained below £26,000 in pessimistic scenarios.

The analysis was based on a trial designed for non-inferiority, although the emtricitabine/tenofovir combination was significantly better than zidovudine/lamivudine in the primary endpoint of viral load > 400 copies/ml at 48 weeks. The correlation between relative risk based on viral load and CD4 cell count was demonstrated. Although there were some concerns with the economic model, overall there was sufficient case to demonstrate cost-effectiveness in treatment-naïve HIV patients.

Patient and public involvement

Patient Interest Group Submission: HIV Scotland

Budget impact

The estimated budget impact in 2006 is £110,000 for 22 patients treated with emtricitabine/tenofovir rising with increasing incidence of newly diagnosed and uptake of treatment to an estimated £1.1 M for 216 patients.

Guidelines and protocols

British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy, 2005 (see clinical effectiveness section).

Additional information

In July 2004, following a full submission, emtricitabine was not recommended by SMC for use in the treatment of HIV-1 infected adults and children. In combination with other antiretrovirals it produces a viral response in treatment-naïve patients and those previously stabilised on other antiretrovirals. However an economic analysis was not provided, thus the economic case is not demonstrated.

In June 2002, following a full submission, tenofovir disoproxil fumarate was recommended in combination with other antiretroviral agents in HIV infected patients over 18 years of age experiencing virological failure. Tenofovir produces a clinically relevant viral response in heavily pre-treated patients experiencing early virological failure. Tenofovir should be initiated under the general supervision of specialists experienced in the management of HIV/AIDS patients.

In August 2003, following a full submission, enfuvirtide was recommended for restricted use in Scotland. It was restricted to use by clinicians experienced in the management of HIV infected patients. It is licensed for use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes, protease inhibitors. non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens.

In April 2005 following an abbreviated submission, SMC accepted abacavir tablets 300 mg for use in a once-daily dosing regimen for treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents over 12 years, in combination with other antiretroviral medicinal products.

In April 2005 following an abbreviated submission, SMC accepted the fixed-dose combination of abacavir 600 mg and lamivudine tablets 300 mg for use in the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents over 12 years, in combination with other antiretroviral medicinal products. Both products are nucleoside reverse transcriptase inhibitors. In patients for whom this combination is appropriate it offers a single tablet at a lower cost per dose compared with the individual components.

In June 2005 following a full submission, fosamprenavir, in combination with low-dose ritonavir was accepted for use within NHS Scotland for the treatment of Human

Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products. It should be prescribed by HIV specialists only.

Advice context:

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

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

This assessment is based on data submitted by the applicant company up to and including 15 December 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Saag MS, Cahn P, Raffi F et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. JAMA 2004;292(2):180-190.

Benson A, van der Horst C, LaMarca A et al. A randomised study of emtricitabine and lamivudine in stably suppressed patients with HIV. AIDS 2004; 18: 2269-76.